INFECTED NON UNION OF LOWER LIMB LONG BONES: A RETROSPECTIVE COHORT STUDY COMPARING OUTCOMES OF METHICILLIN SENSITIVE STAPHYLOCOCCUS AUREUS (MSSA), METHICILLIN RESISTANT STAPHYLOCOCCUS AUREUS (MRSA) AND EXTENDED SPECTRUM BETA LACTAMASE PRODUCERS (ESBL)

A dissertation submitted to the Tamil Nadu Dr M.G.R. Medical University in partial fulfillment of the requirement for the award of M.S. Branch II (Orthopedic Surgery) Degree March 2010-2013

Department of orthopedics

Christian medical college, Vellore

CERTIFICATE

This is to certify that the dissertation entitled '**Infected non union of lower limb long bones: A retrospective cohort study comparing outcomes of Methicillin Sensitive Staphylococcus aureus (MSSA), Methicillin Resistant Staphylococcus aureus (MRSA) and Extended Spectrum Beta Lactamase producers (ESBL)'** is the bonafid original work of Dr Raju L Hadimani submitted in fulfillment of the rules and regulations for the MS orthopedics examination of the Tamil Nadu Dr. MGR Medical university, to held in April 2013

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This consolidated report presented herein is based on a bonafid IRB approved study conducted by the candidate himself.

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Gurur-Brahmaa Gurur-Vissnnur-Gururdevo Maheshvarah |

Gurure[-I]va Param Brahma Tasmai Shrii-Gurave Namah ||1||

The Guru is Brahma, the Guru is Vishnu, the Guru Deva is Maheswara (Shiva),

The Guru is Verily the Para-Brahman (Supreme Brahman); Salutations to that Guru.

Bearing these beautiful thoughts I humbly offer my work at the feet of my parents through whom I have felt HIS blessing in every step of my life.

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Introduction

Infected non union of lower limb long bones is one of the most common complication following fracture especially open fractures in developing country like India. Open fracture with severe contamination and communition, delay in presentations to hospitals, delay in referrals to trauma care centre, delayed surgical care results in increased number of infected non unions especially in femur and tibia.

Road Traffic Accidents (RTA) in India

World Health Organization (WHO) report on road safety reported that India has highest number of road accidents. With more than 1million deaths annually India has highest road traffic accident rate in world. The risk of being involved in a fatal road traffic crash has increased for Indian citizens over the past few years. This increase is attributed to increase in the number of motor vehicles per capita in India.

Main reason of increasing RTA in India speed driving, long distance driving(truck drivers),drunk and drive, minimal use of helmets, seat belts in vehicles.

A study from one of the Medical College from Pondicherry, on road traffic accidents in India showed that working laborers were the highest (30%) among the victims and highest number of victims (31%) were between 20-29 years of age followed by 30-39 years and 40-49 years age group. About 70% of the victims were under 40 years of age (1). The long distance to work place and poor transport facilities make these people at risk to road traffic accidents.

Industrial accidents

Second cause is industrial accidents. In India where economy is growing fast but our educations system at primary and secondary level is still lagging behind so unemployment and illiteracy dominates among industrial workers and labors, there is small role for ergonomics, lack of proper training, poor safety measure at work place, long duration of work and lack of concentration while working complicate in accidents.

Cigarette smoking has been shown in numerous clinical and experimental studies to have an adverse effect on fracture-healing (3) . Smoking places the patient at a risk of delayed union and increases the rate of complications. Previous smoking history also appears to increase the risk of osteomyelitis and delayed time for union (4).

Infected non union of the lower limbs is significant problem both to patients and treating orthopedician. In many instances patient had already undergone multiple surgical procedure, lost his or her considerable money and time, lost his job, alter his life style, sad and depressed. Multiple surgeries are not only physical trauma but also psychological . The problems faced by treating orthopedician are not less.

Infection with polymicrobial organism, multiple scars of old surgeries, contractures of skin and soft tissue, edema, poor neurology and vascular supply, persisting draining sinuses and osteoporosis of bone further compromise and complicate the surgical planning and procedure.

Persisted infection, deformity, shorting of the limb, joint stiffness disability complicates the non union. Conventional method of treatment of infected non union includes extensive debridement and soft tissue coverage with flaps and or skin graft, antibiotic impregnated beads packing in the defect to increase the local concentration of the antibiotics without systemic side effects, papineau open cancellous bone grafting, free tissue transfer addresses both non union and infection . Secondary procedure are usually required to correct deformity, bone loss, shortening, joint contracture and to provide stability.

Most of these challenges are addressed by Ilizarov and to some extent by limb reconstruction system(LRS).

Evidence has been accumulating that infections produced by Methicillin-resistant Staphylococcus aureus(MRSA) are more virulent and more deeply invasive than those produced by Methicillin-sensitive Staphylococcus aureus(MSSA). Methicillin-resistant Staphylococcus aureus infection is costly to treat, has a high mortality and morbidity and results in longer hospitalization compared to Methicillin susceptible Staphylococcus infection(2)

Currently there are no studies which focus on organisms and the clinical, functional and radiological out comes in infected non union of long bone but it has been studied in musculoskeletal infections in general. Musculoskeletal infections caused by MRSA are associated with a longer hospital stay, a greater number of surgical interventions higher complication and mortality rates than those caused by MSSA, as well as with higher rates of deep venous thrombosis, septic pulmonary emboli and abscess formation.

There are no studies in the literature which compares organisms involved in infected non union of lower limb long bones and their clinical, functional and radiological outcomes. This has been well documented in periposthesis infection and joint infections that MRSA are associated with a longer hospital stay, a greater number of surgical interventions, higher complication and mortality rates than those caused by MSSA . The role of the ESBL is also not well documented.

Objectives and aims of study

(A) To determine the clinical, functional and radiological outcomes of infected non union of lower limb long bones treated in Christian Medical College,Vellore between 2007 to 2009 in Department of Orthopedics.

(B) To compare the outcomes between Methicillin-sensitive Staphylococcus aureus (MSSA), Methicillin-resistant Staphylococcus aureus (MRSA) and Extended Spectrum Beta Lactamase producer (ESBL).

(C) To determine whether infections produced by MRSA and ESBL are more virulent, needs multiple procedures , needs more debridement, more time to union and more duration of hospital stay than those produced by MSSA in infected nonunion of long bone of lower limbs.

LITERATURE REVIEW

Definition

Non-union of the fracture is defined as the cessation of all reparative processes of healing without bone union (5). In 1986, for purposes of testing bone-healing devices, United States Food and Drug Administration panel defined nonunion as “established when a minimum of 9 months has elapsed since injury and the fracture shows no visible progressive signs of healing for 3 months.” This criterion cannot be applied to every fracture, however. A fracture of the shaft of a long bone should not be considered a nonunion until at least 6 months after the injury because often union requires more time, especially after some local complication, such as an infection(6).

Infected nonunion has been defined as a state of failure of union and persistent infection at the fracture site for 6 to 8 months(8). Infected nonunion can develop after an open fracture, after a previous open reduction and internal fixation (ORIF) or as a sequel to chronic hematogenous osteomyelitis. The open fracture is the most common cause of infected nonunion and the tibia is the most commonly involved bone in the infected nonunion after an open fracture(9,10). Because of increased enthusiasm for operative fracture surgery, infected nonunion after implant surgery has nearly equal incidence(9).Factors associated with infected nonunion include exposed bone devoid of vascularized periosteal coverage for more than 6 weeks, purulent discharge, a positive bacteriological culture from the depth of the wound, and histologic evidence of necrotic bone containing empty lacunae. Soft tissue loss with multiple sinuses, osteomyelitis, osteopenia, complex deformities with limb-length inequality, stiffness of the adjacent joint and polybacterial multidrug resistant infection all complicate treatment and recovery(9). These factors make an unfavorable milieu for fracture union(8).Even after prolonged treatment and repeated surgeries to correct this problem, the outcome is unsure and amputation may be the only alternative left.

According to the AO-Principles of fracture management, delayed union describes the situation where there are distinct clinical and radiological signs of prolonged fracture healing time. Unless there is bone loss, a non-union is usually declared between 6 and 8 months following the fracture. Pseudarthrosis is defined as formation of a false joint where a fibrocartilaginous cavity is lined with synovium producing synovial fluid(7).

The diagnosis of non-unions is based on clinical symptoms and physical findings including pain at the fracture site and evidence of pathologic motion, as well as the radiological signs that appear during the course of treatment. The radiological signs depend on the type of non-union.

They are generally indicated by the absence of bone bridging between the fragments, persistent fracture lines, sclerosis at the fracture ends, a gap, and hypertrophic or absent callus(7). Final stage of a nonunion is formation of pseudoarthrosis. For radiographic assessment anteroposterior, lateral and oblique views are used.

Etiology

As fracture repair is a continuous process, many biologic and/or mechanical factors play a significant role in the consolidation of a fracture. Non-union may occur either as a result of a poor mechanical or biological environment at the fracture area or as a combination of the two.

Generally, disturbed vascularity and instability are the most important factors leading to a non-union.

The biologic factors are related more to vascularity. Inadequate blood supply can be caused by trauma or surgical disruption or by instability at the fracture site. Open fractures, especially severe grades II and III, or unstable fractures from high energy trauma, are at high risk of developing into a non-union because of unfavourable biologic environment. Poor healing rates also apply to fractures where the bone has inadequate soft tissue coverage, and in conditions, which include bone loss, infection and diminished blood supply. Another cause of fragment avascularity is open reduction of a fracture with wide stripping of the periosteum and damage of the bone and soft tissue blood supply during internal fixation.

Instability at the fracture site is the principal mechanical factor that leads to non-unions. Inadequate immobilization or poor external or internal fixation allows excessive motion at the fracture site. This motion creates initially high strain to the local precursor cells, which are later sensitised by biochemical mediators so that activation and proliferation occur. Generally, the amount of strain affects the multi-stage and multifaceted bone healing process under the control of a mediator system(10).

Local factors were defined in a review at this clinic of 842 patients with nonunions of long bones. Boyd found that nonunion was more common when the fractures were (a) open; (b) infected; (c) segmental, with impaired blood supply, usually to the middle fragment; (d) comminuted by severe trauma; (e) insecurely fixed; (f) immobilized for an insufficient time; (g) treated by ill-advised open reduction; (h) distracted either by traction or by a plate and screws; or (i) of irradiated bone

General factors such as old age, cachexia, malnutrition, anti-inflammatory agents, anticoagulants, steroids, burns and radiation may be contributory, but are not the main causes of nonunion(11).

Cigarette smoking was associated with a higher risk of delayed union, non-union and other complications in patients who smoked compared to non-smoker with open tibial fractures(12).

Additionally, nonsteroidal antiinflammatory drugs (NSAIDs) have been found to decrease fracture healing in multiple animal studies. Several studies have found delayed healing in human subjects who were taking NSAIDs, whereas many other studies refute the hypothesis that NSAIDs delay fracture healing. At best, the literature is still conflicting concerning the influence of NSAIDs on fracture healing

PATHOGENESIS (13)

In a nonunion, the normal fracture repair process occurs only minimally, is interrupted, or does not result in the formation of bridging bone; instead it produces only fibrous tissue or cartilage, which is interposed in the fracture site in the absence of bony callus bridging between the two major fracture fragments. Unless obscured by overlying hypertrophic callus, a radiolucent line representing the zone of fibrous and/or cartilaginous tissue is evident on plain radiographs

When a nonunion is characterized by the production of cartilage in the presence of significant motion, often a cleft will develop in the cartilage. The surrounding fibrous tissue forms a pseudocapsule; with sealing of the bone ends and remodeling, a false joint, or pseudarthrosis, is formed. A serum transudate is usually found in these pseudarthroses, which is evident upon incision through the fibrous capsule into the pseudarthrosis as normal-appearing joint fluid exudes forth. Atrophic and oligotrophic nonunions are characterized by minimal or no formation of cartilage, a predominance of fibrous tissue formation, and what appears to be an aggressive osteoclastically mediated resorption of the bone ends, resulting in a pencil-like configuration of the ends of the major bone fragments. In part, this picture may be caused by actual mechanical erosion of the bone ends resulting from weight bearing or excessive motion. This picture is more common in the presence of pathologic nonunions, such as in congenital nonunions associated with neurofibromatosis

Infection, per se, does not cause nonunion, as union has been shown to occur in the presence of active infection. Uncontrolled infection, however, causes nonunion, predominantly because purulent material dissects under pressure within the intramedullary canal and along the subperiosteal surfaces of bone, resulting in bone necrosis. The inflammatory response to the infectious process may also lead to an excessive remodeling response causing osteolysis, which further slows the rate of union.

The initial event of infection occurs when bacteria successfully lodge on or near the bone or implant. The easiest and most common access for bacteria is the surgical wound. They flourish in this environment because trauma to the tissues by the surgery, causes some tissue necrosis is due to direct trauma, compromises the blood flow to the tissues and results in hematoma formation. The presence of the large foreign body provides a surface for the bacteria to adhere to.

The other routes bacteria may take to reach the area are hematogenous seeding and contiguous spreading from adjacent areas of infection. The hematogenous spread of bacteria has been associated with chronic skin lesions, dental manipulation, urinary infection, diabetes, and other chronic diseases. One of several scenarios may take place once the bacteria have gained entry to the area. Bacteria may be destroyed by the host, live in symbiosis with the host, or flourish, causing local infection, host sepsis, and even death.

The body's first response to bacterial invasion is an acute inflammatory reaction. A myriad of components are involved in this process, including polymorphonuclear cells, chemotactic factors, and the immune system. Leukocyte diapedesis occurs, followed by infiltration of polymorphonuclear cells to the area. The process in which polymorphonuclear cells are attracted to the area by chemical substances is known as chemotaxis.

The immune system is composed of cell-mediated and humoral components. Both cell-mediated and humoral responses are activated to fight bacterial infections. Once the polymorphonuclear cells attack bacteria, some may be damaged, thus releasing additional chemotactic molecules that attract even larger numbers of polymorphonuclear cells. When the polymorphonuclear cells are in proximity to the bacteria, the particles are phagocytosed. For phagocytosis to occur, opsonins or components in the serum must coat the bacteria, making them more attractive for the macrophage.

Elderly patient, may be particularly susceptible to infection because their immune systems are compromised. With increasing age, the immune becomes less competent. These changes include atrophy of the thymus (the site of T-cell maturation), a decreased ability to mount a delayed-type hypersensitivity to various stimuli, and a generalized decreased ability of lymphocytes response to respond to foreign stimuli.

The nonspecific immune response can be affected not only by activation of the complement system but also by certain medications. Nonsteroidal anti-inflammatory agents, steroids, and aspirin are common medications that suppress the immune response.

CLASSIFICATIONS

(I)**Weber-Cech classification**(according to the viability of the ends of the fragments)(21)

Hypervascular nonunions(capable of biological reaction) subdivided :

1. **Elephant foot:** rich in callus, caused by mechanical instability. Increasing the mechanical stability of the fracture site will often permit these to heal

2. **Horse hoof*:*** mildly hypertrophic and poor in callus. Typically occur after a moderately unstable fixation with plate and screws. The ends of the fragments show some callus, insufficient for union, and possibly a little sclerosis.

3. **Oligotrophic :** not hypertrophic, but are vascular, and callus is absent. They typically occur after major displacement of a fracture, distraction of the fragments, or internal fixation without accurate apposition of the fragments.

The second type of nonunion is **avascular** (incapable of biological reaction),a poor blood supply in the ends of the fragments, subdivided as follows:

1. **Torsion wedge:** characterized by the presence of an intermediate fragment in which the blood supply is decreased or absent. The intermediate fragment has healed to one main fragment, but not to the other.

2. **Comminuted :** characterized by the presence of one or more intermediate fragments that are necrotic.

3. **Defect:** characterized by the loss of a fragment of the diaphysis of a bone. The ends of thefragments are viable, but union across the defect is impossible.

4. **Atrophic :**These usually are the final result when intermediate fragments are missing, and scar tissue that lacks osteogenic potential is left in their place. The ends of the fragments have become osteoporotic and atrophic

(II)Gordon and chiu (severity of underlying bone damage)(22)

Type A: tibial defect and non union without significant segmental loss

Type B:tibial defect more than three centimeter long with intact fibula

Type C:tibial defect more than three centimeter long involving both tibia and fibula

(III)May and Jupiter(status of tibial bone after soft tissue and skeletal debridment)(23)

Type I: intact tibia and fibula capable of withstanding functional load. Localized soft tissue loss, unicortical skeletal involvement with little or no threat to the skeletal integrity, rehabilitation is six to twelve weeks type II : intact tibia with bone graft needed for the structural support tibia is still intact but weaken by debridment and may fracture by physiological load

Type III: tibial defect six centimeter or less with intact fibula

Type IV :tibial defect more than six centimeter with intact fibula

Type V : tibial defect more than six centimeter and no usable intact fibula

(IV)**Paley et al.** (classification of nonunions of the tibia , can be applied to other bones).(24)

They divided nonunion, clinically and radio graphically, into two major types :

Type A: nonunion with bone loss of less than 1 cm. subdivided

Type A1: mobile deformity and those with a

Type A2: fixed deformity

Type A2-1: stiff nonunion without deformity

Type A2-2: stiff nonunion with a fixed deformity.

Type B : those with more bone loss more than 1 centimeter

Type B : non unions with a bony defect ,

Type B2: loss of bone length

Type B3: both bony defect and loss of length modified further by the presence or absence of infection.

(V)**Anil K. Jain(**according to the bone gap and severity of Infection)(25) categorized into four groups Type A is infected nonunion of long bones with non draining (quiescent) infection, with or without implant in situ.

Type B is infected nonunion of long bones with draining (active) infection. Both are classified further into two subtypes.

Subtype 1 is bone gap smaller than 4 cm. Subtype 2 is bone gap larger than 4 cm.

The size of the bone gap is assessed after debridement. Patients with wounds that had no discharge for 3 months were labeled as nondraining (quiescent)

Treatment philosophy

Treatment of infected nonunion is technically demanding, prolonged, and needs a team. There are two schools of thought in the treatment of infected nonunion.

(a) The 'union-first' strategy

(b) The 'infection-elimination first' strategy.

The first strategy aims at achieving union first and then dealing with the problem of infection as the problem presents itself. This approach does not aim at eradication of infection as the main objective.

The second strategy aims at elimination of infection as the first and major objective and bone union as the next objective.

The second strategy is the more popular one.

This strategy does have its drawback: bone debridement leads to a defect which dramatically increases the complexity of reconstruction.

The strategy has two steps:

(a) Radical debridement of necrotic tissue (bone and soft tissue).

(b)Reconstruction of bone (to effect union) plus soft tissue (to provide healthy viable coverage).

The bone defect (dead space) that results from bone debridement can be managed by antibiotic-impregnated bone cement. Once infection is eradicated or controlled, the second stage is commenced

There are four operative techniques (with considerable overlap among them) which have been used :

(I) Ilizarov.

(II) Intramedullary devices with or without the use of external fixator.

(III) Free tissue transfer.

(IV) In situ reconstruction.

Bone results are, in general, better compared to functional results. Overall, the outcome following treatment of infected nonunion are good to excellent

Change in trend of Methicillin-resistant Staphylococcus aureus (MRSA) infection

Methicillin-resistant Staphylococcus aureus (MRSA) was described in 1961, shortly after the introduction of methicillin, and outbreaks of MRSA were reported in the early 1960s . Since that time, MRSA has spread worldwide, and the prevalence of MRSA has increased in both healthcare and community settings. For example, the prevalence of methicillin-resistance among S. aureus isolates in intensive care units in the United States is 60 percent(26), and more than 90,000 invasive infections due to MRSA occurred in the United States in 2005(27)

DEFINITION — Methicillin resistance requires the presence of the mec gene; strains lacking a mec gene are not methicillin resistant. Methicillin resistance is defined in the clinical microbiology laboratory as an oxacillin minimum inhibitory concentration (MIC) ≥4 mcg/mL(28).Other methods of detection, such as the use of the cefoxitin disk or one of several polymerase chain reactions (PCR) to detect the mec gene, are also used.

Isolates resistant to oxacillin or methicillin are also resistant to all beta-lactam agents including cephalosporins. MICs of 4 to 8 mcg/mL are considered to represent borderline or low level resistance.

Evolving epidemiologic observations

The CA-MRSA and HA-MRSA classifications are no longer distinct, since patients can develop MRSA colonization in one realm and develop manifestations of infection in another

The blurring epidemiologic distinction between HA-MRSA and CA-MRSA was also illustrated by the United States Active Bacterial Core surveillance network report of 8987 invasive MRSA infections in 2005. In this report, the rate of invasive MRSA infection was 32 per 100,000, the incidence of MRSA among patients ≥65 was 128 per 100,000 and the mortality rate was 6.3 per 100,000 (29)

Is Methicillin-Resistant *Staphylococcus aureus* More Virulent than Methicillin-Susceptible *S. aureus?*

Comparative studies regarding the epidemiology and outcomes of localized orthopedic implant-related infections stratified by staphylococci or type of orthopedic implant are rare

Staphylococcus aureus is a virulent pathogen and the most common cause of surgical site infection and also more commonly seen in orthopedic implant related infection and non unions Methicillin resistance further complicates therapy for *S. aureus* . The prevalence of MRSA has increased dramatically since it was first described in the 1960s

Methicillin-resistant *Staphylococcus aureus* (MRSA) is an increasingly common pathogen in surgical site infection (SSI) but the independent contribution of methicillin resistance to the outcomes for patients with *S. aureus* infection is unclear because patients who develop MRSA infections are typically older and sicker than are patients who develop methicillin-susceptible *S. aureus* (MSSA) infection

Dorota Teterycz(31) studied outcomes of orthopedic implant infections due to different staphylococci. There were 44 infections due to MRSA, 58 due to MSSA, and 61 due to

CoNS. Overall cure was achieved in 57% of MRSA infections, 72% of MSSA infections, and 82% of CoNS infections, after a minimum follow-up of 1 year. In the subgroup of arthroplasty infections only, cure was achieved in 39% of MRSA, 60% of MSSA, and 77% of CoNS episodes. They concluded that in orthopedic implant infections, S. aureus is more virulent than CoNS. MRSA has the worst outcome and CoNS the best

Materials and methods

This study is retrospective cohort study done on patients with infected non union of lower limb long bones, both tibia and femur, treated in Department of Orthopedics Christian Medical College, Vellore between years 2007 and 2009.

Fracture non union was defined according to **Dendrinos et al** (33) A fracture that has been un-united for less than six months (<6months) was defined as non union if the wound was open, infected and there was exposed dead bone or metal.

A fracture also considered to be non union after six months (≥6months) if there was clinically apparent motion at the fracture site and discharging sinus indicating the presence of dead bone or sequestrum.

Criteria for presence or absence of clinical infection. **(Simpson et al)** (36)

1. Criteria for presence clinical infection. Open wound or draining sinus is present pre-operatively or frank pus found at the time of operation.

2. Criteria for absence of infection.

    No overt signs of infection present pre-operatively.

    No history of open wound or multiple previous surgeries.

    No post-operative infection for at least 1 year after operation.

Inclusion criteria

1. Age above 18years at time of presentation.

2. All patients of infected non union of long bone lower limb treated in CMC between 2007 to 2009 with debridement and internal or external fixator.

3. Culture positive for Methicillin-sensitive Staphylococcus aureus (MSSA), Methicillin-resistant Staphylococcus aureus (MRSA) and Extended Spectrum Beta Lactamase producer (ESBL).

4. Persisting discharging sinus for at least 3 months.

5. Dendrinos definitions for non union and Simpson definition of clinical presence or absence of infection.

Exclusion criteria

1. Pathological fractures (secondary to osteoporosis, osteopenia, metabolic bone disease, tumor).

2. Patients with Osteomyelitis who developed fracture.

3. Stress fractures.

4. Age less than 18 years.

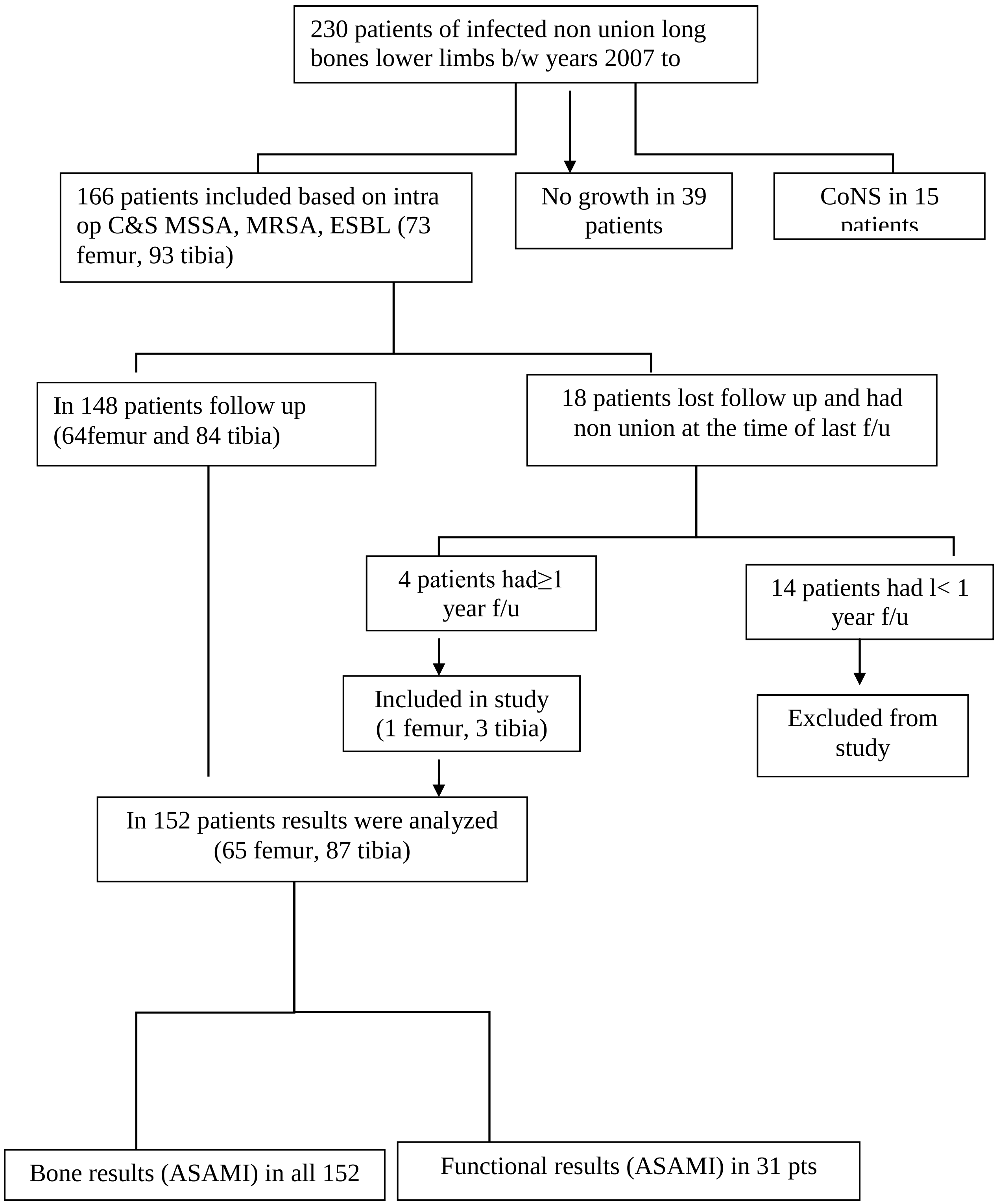
5. Patients with co infection of MSSA and ESBL (because of small sample size).

6. Other infections (Coagulase Negative Staphylococcus species CoNS, Tuberculosis, Fungal infections etc)

Patient selection

The information about the patients were collected from Out patient charts (OP), Inpatient charts (IP), operative notes, discharge summaries, blood investigations, intra operative pus and tissue culture and sensitivity reports, radiological examinations, telephone interviews, letters to patients and regular follow up of patients in Out patients department(OPD).

Between the years 2007 and 2009 there were 230 patients with infected non union long bone lower limbs (110 patients with infected non unions femur and 120 patients with infected non unions of tibia) treated in our hospital, among them 152 patients with infected non unions long bone lower limbs were included in the study(65 patients with infected non union femur and 87 patients with infected non union tibia) based on growth of the interested organisms(MSSA,MRSA and ESBL) from the intra operative culture and sensitivity. Patients with no growth or growth of other organism were excluded from the study. Patients with intra operative culture with co-infection of MSSA plus ESBL (8 cases) were also excluded from the study due to smaller sample size.


230 patients of infected non union long bones lower limbs b/w years 2007 to
166 patients included based on intra op C&S MSSA, MRSA, ESBL (73 femur, 93 tibia)
No growth in 39 patients
CoNS in 15 patients
In 148 patients follow up (64femur and 84 tibia)
18 patients lost follow up and had non union at the time of last f/u
4 patients had≥1 year f/u
14 patients had l< 1 year f/u
Included in study (1 femur, 3 tibia)
Excluded from study
In 152 patients results were analyzed (65 femur, 87 tibia)
Bone results (ASAMI) in all 152
Functional results (ASAMI) in 31 pts

Patient information

There were total of 152 cases of infected non union long bone lower limbs included in the study among them 65 cases of infected non union femur and 87 cases of infected non union tibia. There were 141 male (93%) and 11 female (7%). Age of the patients ranged from 18 to 69 years with mean of 36.8 years and SD 12. 58(39.2%) patients were between 18 to 30years.

Road traffic accidents was the most common mechanism of injury present in 123(82%) patients and second mechanism was fall from height in 13(9%) patients.

Since this is tertiary care centre and most of our patients were from far places from West Bengal, Jharkhand, Chattisgarh, Bihar and Bangla Desh, and they were initially treated in other local hospitals and after intra venous antibiotic course and multiple procedures patients came to our hospital for the further management.

Place of injury in 105(71%) patients was out side Tamil Nadu and only 43(29%) patients were from Vellore. For the same reason initial treatment and surgical procedures were mainly done out side the CMC.

Most of our patients were relatively young and not associated with major illness. Only 16 (11%) patients had diabetes mellitus and 5 (3.8%) patients were having history of chronic smoking.

Pre operative work up

When patients with infected non union comes to our hospital, in our out patient department we clinically examine the patients beside the complete history and general examination we concentrate on the limb as whole, look for soft tissue condition, discharging sinus, scar of the previous surgeries, deformity, limb length discrepancy, stiffness of the joint, distal tropic changes, signs of reflex sympathetic dystrophy and most important neurovascular status of the limb.

We found out the cause of non union. In most of the cases it was active infection and instability at the fracture site and we treated both of them. We discussed the various methods of treatment options with patients and explain them approximate durations each treatment, number of surgeries, staging the procedures, need for the multiple surgeries including bone grafting, complications and psychologically prepared the patients.

We took pus for culture and sensitivity, blood and radiological investigations. Then according to the type of infection, type of non union ,soft tissue condition and bone affected we planned our treatment.

Most of patients who came to CMC had already undergone some primary procedures, debridement and internal or external fixation elsewhere .We sent intra operative deep sample of the pus, granulation and tissue. If there is no frank pus or granulation we sent the tissue between and surrounding the non union site keeping in mind of subclinical infection locally.

Operative procedures

According to the patients and non union we categorize them and plan for either single or staged procedure.

All of our patients had received one or combination of these seven categories

(1) debridement and internal fixation

(2) debridement and antibiotic beads

(3) debridement and implant exit

(4) debridement , implant exit and internal fixation

(5) debridement, implant exit and antibiotic beads

(6) debridement and limb reconstruction system

(7) debridement and Ilizarov fixator application

Antibiotic beads: This is to deliver levels of antibiotics locally in concentrations that exceed the minimal inhibitory concentrations(MIC). The aim is to increase local concentrations of antibiotic 200 times higher with low systemic toxicity.

We used 2 to 4 g of vancomycin or meropenam to each pack if previous culture shows gram positive cocci (MRSA or MSSA) or we add gentamycin if culture is gram negative bacilli

We routinely take out antibiotic beads between 4 to 6 weeks after insertion.

Operative procedure performed

Out of 152 patients definitive fracture fixation was done with limb reconstruction system (Ortho fix) in 69(45%) patients, Ilizarov fixator in 75(49%) patients, internal fixation in 4 patients and 4 patients underwent amputation.

Patient selection

We divided our patients in to 4 category based on the intra operative culture and sensitivity.

We categorized them in to category I Methicillin-sensitive Staphylococcus aureus (MSSA), category II Methicillin-resistant Staphylococcus aureus (MRSA),category III Extended Spectrum Beta Lactamase producer (ESBL), and category IV co infections of MRSA plus ESBL.

This was based on intra operative first culture and sensitivity report. In our study there were 12(8.1%) patients with MSSA, 39(25%) patients with MRSA, 75(50.6%) patients with ESBL, 26(16.2%) patients have grown MRSA and ESBL

	Femur	tibia	total
MSSA	6	6	12
MRSA	19	20	39
ESBL	28	47	75
MRSA+ESBL	12	14	26
	65	87	152

Type of initial fracture pattern:

Out of 152 patients studied 30(20%) patients had closed fracture and 122(80%) had open fracture (among open fracture 37(24%) patients had type IIIB open fracture according to Gustilo and Anderson classification and in 58(39%) patients exact type of open fracture pattern could not able to record.

Bones affected:

Out of 65 patients of femur fracture, 49 patients had isolated femur fracture, 12 patients had associated with ipsilateral tibia fracture and 4 patients had associated with contra lateral tibia fracture. Similarly out of 87 patients of tibia 72 patients had isolated fracture tibia, 10 patients had ipsilateral femur fracture and 5 patients had contra lateral femur fracture initially.

More than 35% of the patients have had at least 2 surgical procedure before presenting to us

Definitions

(1) Resolution of infection: Resolution of the infection was defined as, when patients had no fever, no pain, no discharging sinus and there were no local signs of infection like local rise of temperature, tenderness and skin condition was normal and the fracture union was in progress.

The patients with discharging sinus at the time of presentation were grouped as having active infection and those with at least 3 months of discharging sinuses initially which later become quiescent were grouped as having quiescent infection.

(2) Union: The fracture was considered as united when it appeared so roentgen graphically, when there was no motion at the fracture site after loosening of the connecting rods and when patient was able to walk without pain and had feeling of solidity of the limb.

(3) Debridement: Debridement included removal of all the skin, fascia, and muscle which was not looking healthy and appeared necrotic. Sequestrum and infected implant also were removed and granulation was curetted out. The ends of the bone were excised till the fresh bleeding bone was visible all around. Almost all our patients required initial debridement.

We divided our patients in to two categories. First category, patients who required 1 to 2 debridement and second, patients who required more than two debridement.

(4) Post debridement bone loss: We compared the pre operative and post operative radiographs and measured the amount of bone that has been resected.

We divided our patients into two categories, up to 30mm bone debrided and more than 30 mm bone debrided.

(5)Bone graft: Bone grafting was planned when there was gap at the fracture site, there were no signs of progression of the union and there were no signs of infection. Ipsilateral iliac crest was usual donor site for bone graft.

(6)Refracture: Refracture was defined as fracture according to treating surgeon united and fixator was removed, and patients were asked to bear partial and complete weight with or without crutches, then if patient sustained fracture secondary to insignificant trauma due to weakness at fracture site is considered as re fracture.

(7)Time to union: In our study most of the patients were from other states (105 patients out of 152,nearly 71%). Most of them undergone several procedures but fracture had not united.

We treated them with debridement and internal or external fixation.

Dendrinos, Kontos S (33) calculated time to union from the day that the intercalary segment came in contact with the target segment, in treatment of infected non union tibia treated with

Ilizarov fixator. But this can not applied to the patients which are not treated with Ilizarov fixator.

We considered time to union from day when definitive fixation was applied to till fracture is completely united according to treating surgeon and fixator was removed.

We divided our patients into two categories, first in which union time was up to 18 months, second union time was more than 18 months.

(8)Soft tissue procedure: Patient who had soft tissue defect and bone was exposed, they were covered with flap cover. Proximal one third defect with exposure of the large part of the proximal tibia were covered with medial or lateral gastrocnemius and for smaller area local rotation flap. For lower third exposed tibia we used local rotation flap for smaller defect and reverse sural artery flap larger defect.

(9)Number of secondary procedure: These are the secondary procedures after the definitive primary fixation. They were divided in to minor and major procedures. Minor procedures included split thickness skin graft (STSG), addition of pins, removal of pins and major procedures included second debridement and wash out, flap cover, fixator realignment. But in the analyzing the data we combined them and analyzed.

(10) Duration of Inpatient (IP) admission: This included the total period of hospital admission in weeks, which was directly proportional to the number of hospital admission, number of procedures and complications.

We divided our patients into three categories. First category, patient who had up to 2 weeks of hospital admission. Second category, patients who had 2-6weeks of hospital admission and third category, patients who had more than 6 weeks of hospital admission.

(11) Inpatient (IP) economic cost: This included the total cost of the treatment including intravenous antibiotic and surgical procedures. Patients who had multiple procedures, multiple hospital admissions, long duration of intravenous antibiotics were assumed to had more hospital bill at end of the treatment .

We divided our patients into three categories. First category patients, who had upto 0.75 lakhs.

Second category patients, who had 0.76-2 lakhs and third category patients who had more than 2 lakhs.

(12) Loss of follow up:

When patients did not attend out patients department regularly and had non union.

They are categorized in to two categories, first category had loss of follow up in less than 12 months and second category had loss of follow up more or equal to 12 months.

Surgical interventions

Out of 152 patients definitive fracture fixation was done with limb reconstruction system (Ortho fix) in 69(45%) patients, Ilizarov fixator in 75(49%) patients, internal fixation in 4 patients and 4 patients underwent amputation.

Surgical technique (Ilizarov)

Ilizarov ring was constructed pre operatively after assessing the patient and radiographs. At surgery under appropriate anesthesia the non union was exposed and radically debrided inclusive of skin, fascia, and muscle. Sequestrum and implant were removed and granulation was curetted out. The ends of the bone were excised till the fresh bleeding bone was visible all around. Whenever gap was less 2 cm, acute docking was done after correcting the angulations. The frame was fixed to the bone with at least 2 k wire per ring. All k wires were tensioned before fixing to ring. Additional schanz pins were used to improve stability whenever necessary.

Whenever non union was close to the ankle joint, ankle spanning fixator was used. The corticotomy was done at the level of metaphysis, after carefully separating the periosteum from bone by circumferential drill holes made in the bone with 2.5mm drill bit which were later joined together using osteotome to complete the osteotomy. While inserting k wire care was taken to abide by safe zone and k wires were stimulated by low voltage current to detect proximity of wires to nerve.

Type of the treatment given

Most of the patients had in one of these treatment Unifocal osteosynthesis which involve debridement and ilizarov ring application.

1. Bifocal osteosynthesis with only bone transport.

2. Distraction combined with gradual docking.

Soft tissue cover

Patient who had soft tissue defect and bone was exposed, they were covered with flap cover. Proximal one third defect with exposure of the large part of the proximal tibia were covered with medial or lateral gastrocnemius and for smaller area local rotation flap, for lower third exposed tibia we used local rotation flap for smaller defect and reverse sural artery flap larger defect.

In our patients out of 152 patients 20 patients required flap cover all in tibia group (12 local rotation flap,3 lateral gastrocnemius, 2 medial gastrocnemius and 3 reverse sural artery flap) and non of the femur group required flap cover.

Post operative protocol

Post operatively distraction was started between 7^{th} to10^{th} post operative day at the rate of 1mm per day. The patient were taught about the distraction, pin site care and physiotherapy of adjacent joints. In patient who showed hypotrophic regenerate and communition during corticotomy were advised to distract 0.5mm per day. When distraction was combined with gradual docking, the docking at the fracture site was at the rate of 1 cm in three days interval and distal neuro-vascularity were monitored through the distraction.

Weight bearing ambulation was taught with crutches in a week time and were encouraged to bear full weight during the treatment.

During the bone transport regular radiographs were taken after weeks of distraction to confirm the transport and later repeated after 3 to 4 weeks to assess the type of regenerate. After the completion of the distraction, ring was kept for about twice the time taken to distraction and x rays were taken regularly. After the consolidation the ring was removed and below knee patellar tendon bearing cast was applied for 4-6 weeks.

During the treatment patients were emphasized about physiotherapy and encouraged to move the proximal and distal joints out the ring. If there was evidence of equines deformity, tendoachillis(TA) stretching and if required TA lengthening was done.

Finally when there was evidence of fracture union the dynamisation of the ring fixator was done and patients were advised to continue full weight bearing. Bone grafting was done when there is evidence of hypotrophic regenerate.

Short course of antibiotics and pin tract injections using gentamycin were give for pin tract infection.

The total duration of the treatment ranges from 7 months to 36 months The complications were divided in to obstacles, problem and true complications During the follow up the following outcome analyzed.

1. Union
2. Complications
3. Bone result
4. Functional result

Complications:

Problems were defined as the difficulties which resolved completely before the fixator was removed by non operative means.

Obstacles were defined as difficulties which resolved completely before the fixator was removed by operative means.

True complications were defined as problems that persisted even after fixator removal. The true complications were divided as minor (that did not affect the out come significantly) and major (that affects out come significantly).

Bone result: According to ASAMI protocol bone results were divided in to excellent, good, fair, poor considering the union, effectively controlled infection, deformity less the 7 degree and limb length discrepancy less than 2.5cm

1. Excellent: Union, no infection, deformity < 7°, limb-length discrepancy < 2.5 cm

2. Good: Union + any two of the following: absence of infection, < 7° deformity and limb-length inequality of < 2.5 cm

3. Fair: Union + only one of the following: absence of infection, deformity < 7° and limb-length inequality < 2.5 cm

4. Poor: Nonunion/re-fracture/union + infection + deformity > 7° + limb-length inequality > 2.5 cm for statistical analysis we combined excellent and good results in to one group and fair and poor into another and compared

Functional results: According to the ASAMI protocol functional results were divided in to excellent, good, fair, poor and failures

Functional results.

1. Excellent: Active, no limp, minimum stiffness (loss of < 15° knee extension/< 15° dorsiflexion of ankle), no reflex sympathetic dystrophy (RSD), insignificant pain

2. Good: Active, with one or two of the following: limp, stiffness, RSD, significant pain

3. Fair: Active, with three or all of the following: limp, stiffness, RSD, significant pain

4. Poor: Inactive (unemployment or inability to return to daily activities)

5. Failures: Amputation

For statistical analysis we combined excellent and good results in to one group, fair and poor into second and amputation as third

RESULTS

The biostatistical analysis is conducted using **Chi square test**

Observations and Results:

The objective of this study was to compare different type of organism and their out come in infected non unions of the lower limbs.

(A)We analyzed our results using ASAMI score for bone results and ASAMI score functional results

(B)Other out comes assessed were (Modified bone results)

(1) Resolution of infection

(2) Union

(3) Number of debridement

(4) Post debridement bone loss

(5) Bone grafting

(6) Re fracture

(7) Time to union

(8) Soft tissue cover

(9) Number of secondary procedure

(C) Secondary out comes of the study

(1) Total number of in patient (IP) stay.

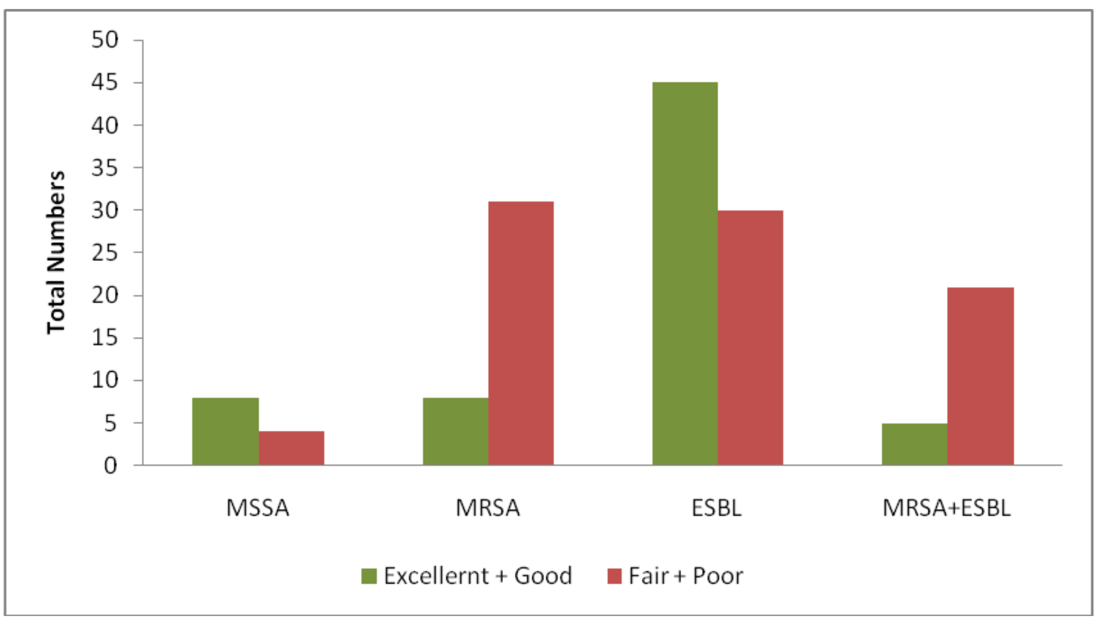
(2) Inpatient economic cost.

Bone results using ASAMI score

		1	2	TOTAL
FEMUR + TIBIA	MSSA	8 (67%)	4 (33%)	12
	MRSA	8 (20%)	31 **(80%)**	39
	ESBL	45 (60%)	30 (40%)	75
	MRSA+ESBL	5 (21%)	21 **(81%)**	26
	TOTAL	66 (44%)	86 (57%)	152

Bone results : 1(excellent and good) 2 (fair and poor)

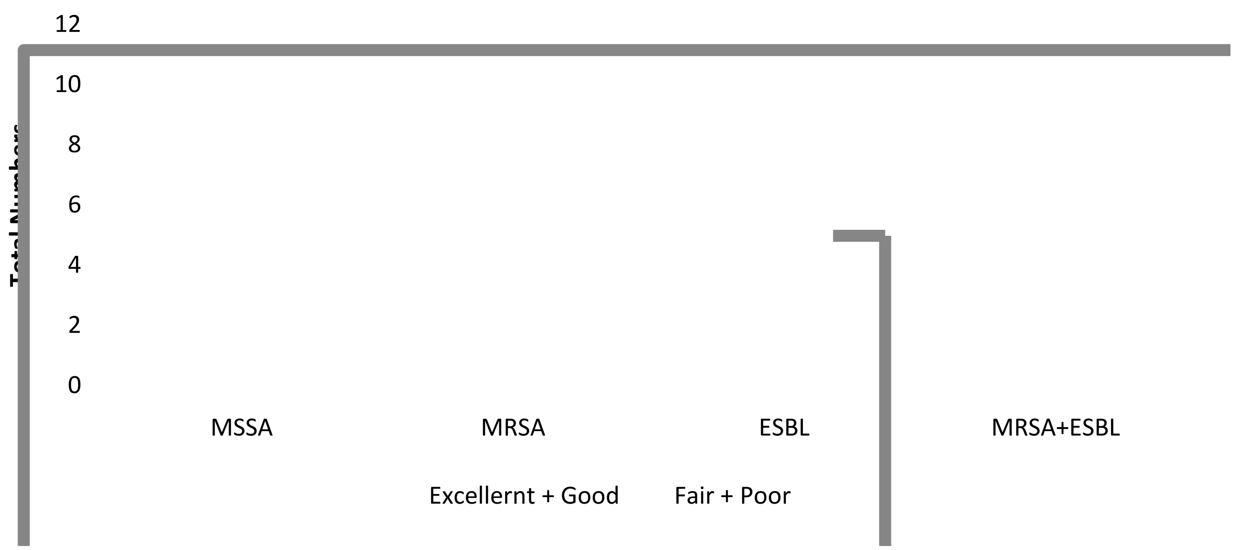
Bone Results



Functional results using ASAMI score

BONE	ORGANISM	FUNCTIONAL RESULTS			TOTAL
		1	**2**	**3**	
FEMUR + TIBIA	MSSA	2**(100%)**	0	0	2
	MRSA	4(44%)	2(22%)	3(33%)	9
	ESBL	10(71%)	4(29%)	0	14
	MRSA+ESBL	2(33%)	3(50%)	1(17%)	6
	TOTAL	18(58%)	9(29%)	4(13%)	31

Functional results 1(excellent and good) 2 (fair and poor) 3 Amputation



Bone results using ASAMI score:

Bone results are available for all the 152 patients. Among them 66(44%) patients had excellent to good results and 86(57%) had fair to poor results. In individual category patients with MSSA 8(67%) had excellent to good out come. 31(80%) patients with MRSA and 21(81%) patients with combined MRSA and ESBL had fair to poor out come

Functional results were studied using ASAMI score:

Among 152 patients treated between 2007 to 2009, we followed up 31 patients in whom functional results are available. 2 patients had MSSA infection, 9 patients had MRSA infection, 14 patients had ESBL infection and 6 patients had co infection of MRSA and ESBL. Results were studied using ASAMI score. For comparison we combined excellent and good results in to one group and fair and poor in to another. Amputation group was kept separately.

From the table it is clear that overall 18(58%) patients had excellent to good results and 9(29%) patients had fair to poor results. Total 4(13%) patients had undergone amputation. Among individual categories all the patients with MSSA 100%(2/2) has excellent to good results. In MRSA category 4(44%) patients has excellent to good results and 2(22%) patients has fair to poor results. In ESBL category 10(71%) patients has excellent to good results and 4(28.6%) has fair to poor results. In co infection of MRSA and ESBL 2(33.3%) patients has excellent to good results and 3(50.0%) patients has fair to poor results.

Out of 31 patients 4 patients under gone amputation. We clinically examined 27 patients and found that 10 patients still had mild pain after walking, in 5 patients infection is still persistent, 17 patients had limp,10 patient had stiff knee, 4 patients had limb length discrepancy up to25mm and 2 patients had 50mm required foot were modification,4 patients had signs of reflex sympathetic dystrophy and edema , 2 patients unemployed and 23 patients retuned to previous occupation.

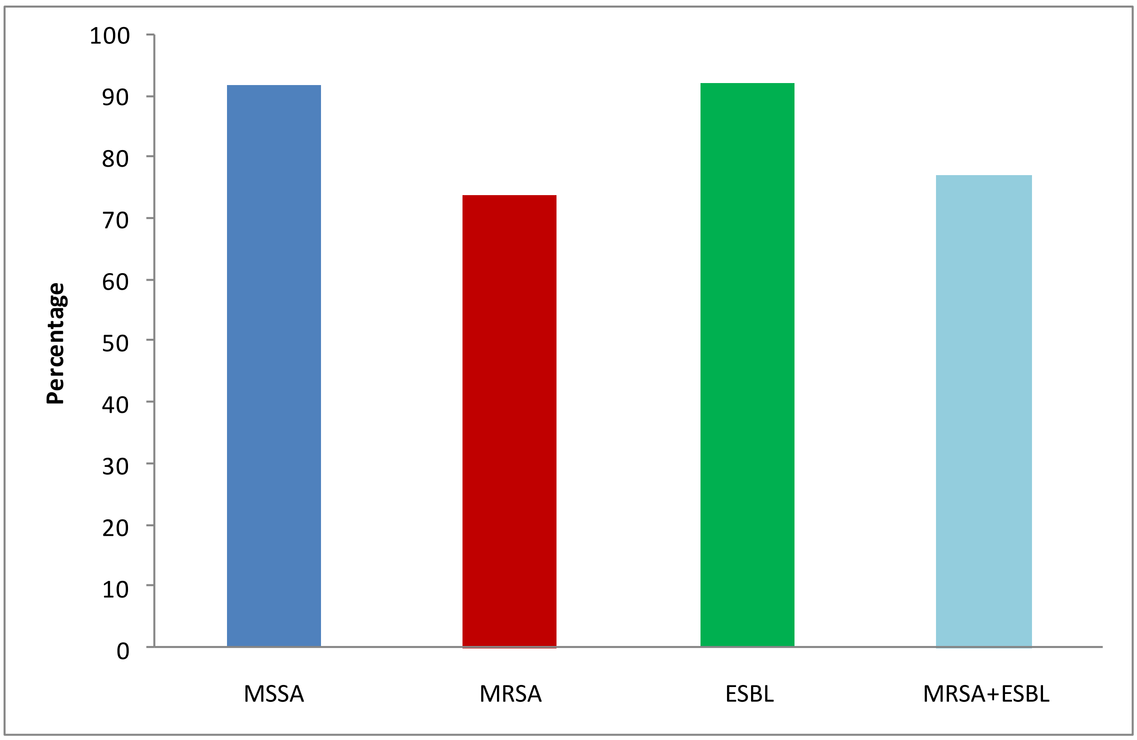
Amputation: Out of 4 patients of amputation 3 belong to MRSA group and one to co infection of MRSA and ESBL group. Reasons for the amputation were chronic discharging sinus, shorting, pin tract infection, large necrotic bone exposed and unhealthy soft tissue.

Three patients out of four under went primary amputation without primary procedure, one patient initially applied ilizarov but due to active discharging sinus, pin tract infection and non union and unstable knee requested amputation

Modified bone results-1

BONE RESULTS	MSSA(12)	MRSA(39)	ESBL(75)	MRSA+ESBL(26)	TOTAL(152)
Resolution of infection	11(92%)	29(74%)	69(92%)	20(77%)	129(85%)
Union	10(83%)	34(87%)	67(89%)	21(81%)	132(87%)

Resolution of Infection



Resolution of infection:

In our study out of 152 patients 129 (85%) have complete resolution of the infection. Resolution of the infection is better in the MSSA (92%) and ESBL (92.0%) group, but in MRSA group only 29 out of 39 patients(74%) had complete resolution worst among the four group.

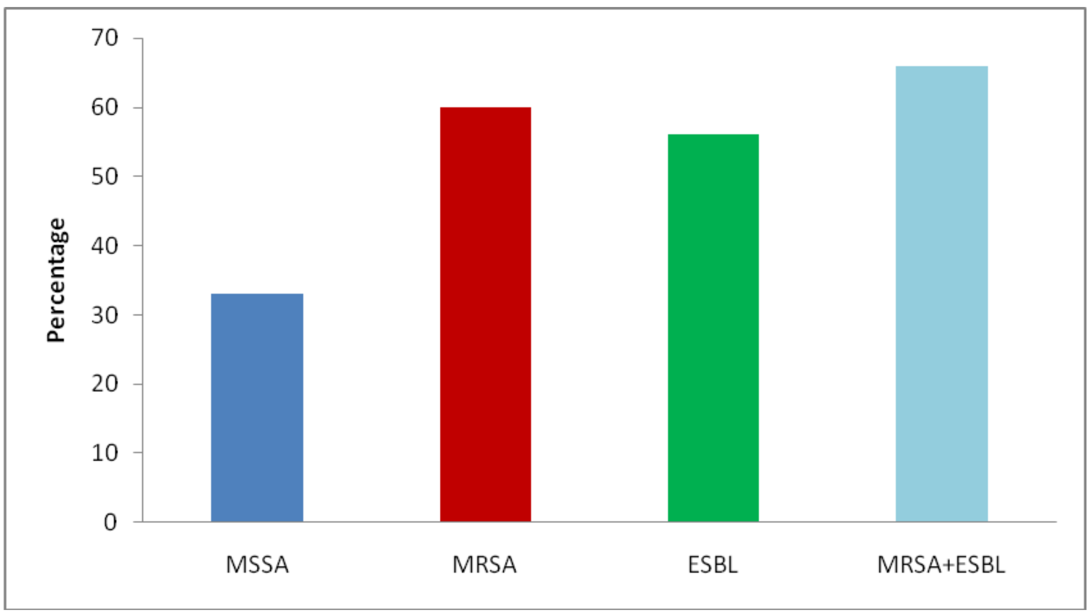
Union:

Out of 152 patients in 132(87%) patients fracture completely united. There is no much difference in the percentage of union among the different organism. Union percentage were highest in patients with ESBL infection(89%) and least in patients with co infection of MRSA and ESBL(81%).

Modified bone results-2

BONE RESULTS		MSSA (12)	MRSA (39)	ESBL (75)	MRSA+ESBL (26)	TOTAL (152)
Number of debridement	1	8(67%)	16(41%)	33(44%)	9(34%)	66(43%)
	2	4(33%)	23(60%)	42(56%)	17(66%)	86(57%)

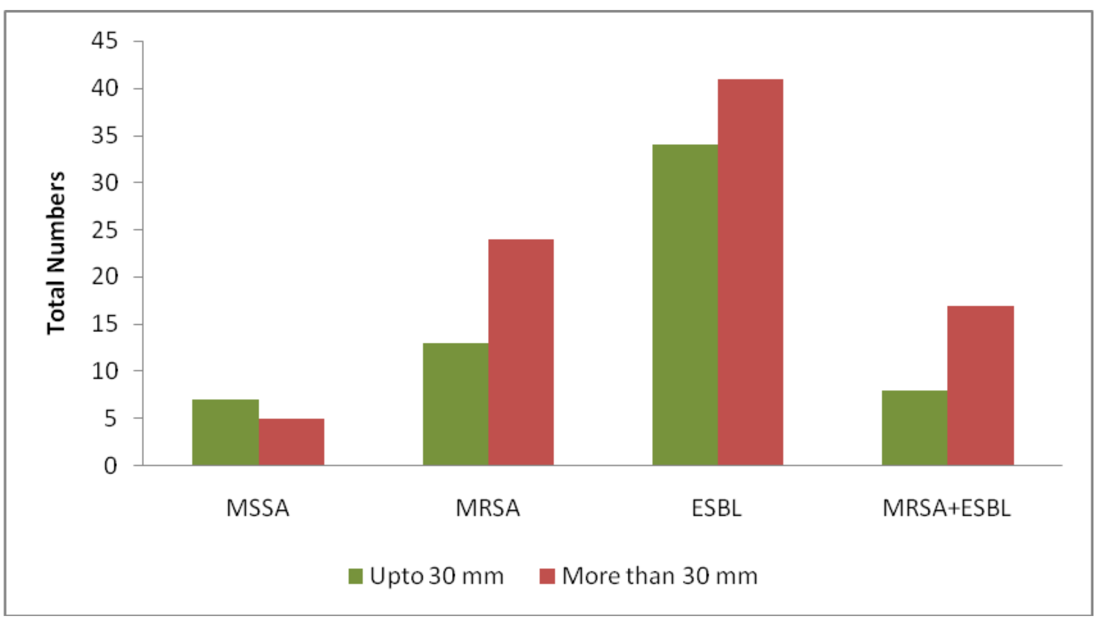
Number of debridement more than 2



Modified bone results-3

BONE RESULTS		MSSA (12)	MRSA (39)	ESBL (75)	MRSA+ESBL (26)	TOTAL (152)
Post debridement bone loss	Upto 30mm	7(58%)	13(35%)	34(45%)	8(32%)	62 (42%)
	More than 30mm	5(42%)	24(65%)	41(55%)	17(68%)	87(58%)

Post debridement bone loss



Number of debridement:

In our study number of debridement ranges from 1 to 8 with mean 2.57. Overall 66(43%) patients required upto two debridement and 86(57%) required more than two debridement**.** In MSSA group 8 out of 12 patients (67%) requited one to two debridement, but in other group nearly 60% of the patients required more than 2 debridement procedure. Two patients of MRSA even required more than four debridement to completely resolve the infection

Post debridement bone loss:

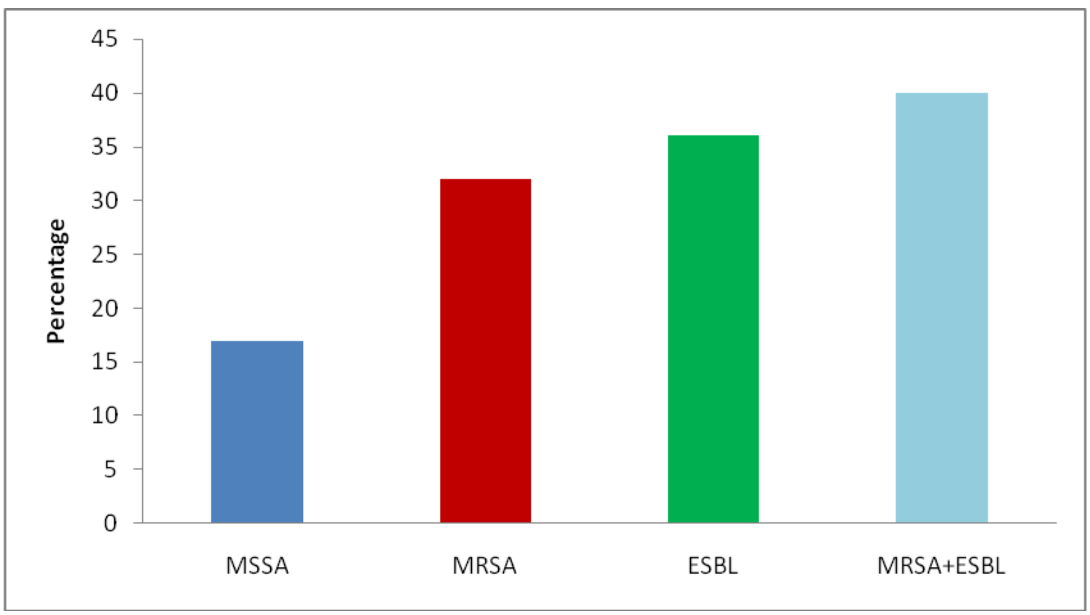
In our study post debridement bone loss ranges from 0 to 71 mm with mean of 36.39mm and median 36mm.Out of 152 patients 62(42%)patients had undergone bone resection up to 30mm and 87(58%) patients required more than 30mm bone resection to completely remove the necrotic tissue. Thus about 60 percent of our patients had more than 30mm post debridement bone loss.

Within the groups 58 percentage of MSSA group had less than 30mm of post debridement bone loss, and more than 65 percentage of patients with MRSA and co infection of MRSA and ESBL had more than 30mm of post debridement bone loss.

Modified bone results-4

BONE RESULTS	MSSA(12)	MRSA(39)	ESBL(75)	MRSA+ESBL(26)	TOTAL(152)
Bone grafting	2(17%)	12(32%)	27(36%)	10(40%)	51(34%)
Refracture	0	6(15%)	7(9%)	3(12%)	16(11%)

Bone Grafting



Bone graft:

Among 152 patients 51 (34%) patients required bone grafting procedure. In MSSA group only 2patients(17%) patients required bone grafting but in other groups it was more than30 percent.

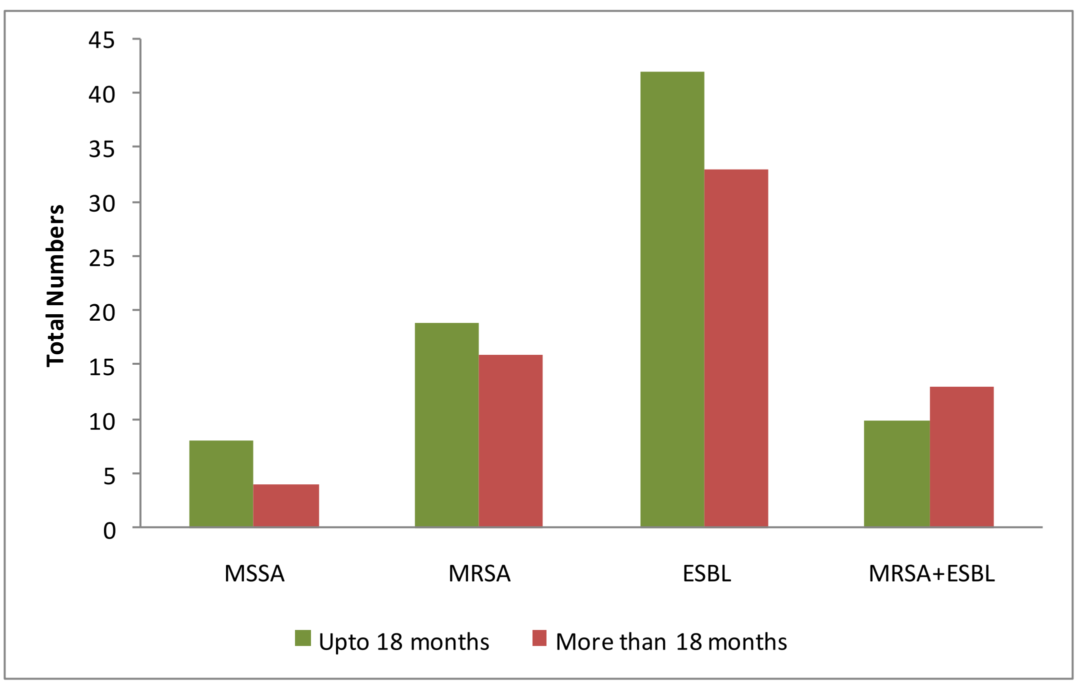
Refracture:

In our series out of 152 patients 16(11%) patients had refracture. Refracture percentage was more is MRSA group about 15 percent (6 out of 39), none of the MSSA group had refracture

Modified bone results-5

BONE RESULTS		MSSA(12)	MRSA(39)	ESBL(75)	MRSA+ESBL(26)	TOTAL(152)
Time to union	UPTO 18MTHS	8(67%)	19(49%)	42(56%)	10(38%)	79(52%)
	More than 18MTHS	4(33%)	16(41%)	33(44%)	13(50%)	66(43%)
Soft tissue cover		1(8%)	4(11%)	11(15%)	5(19%)	21(14%)
Number of secondary procedure		8(67%)	30(81%)	63(84%)	22(92%)	123(83%)

Time to union



Time to union:

In our study time to union rages from 5months to 55 months with mean of 20.1 months and median of 15.5 months.

Overall in 79(52%) patients fracture united within 18 months of period and 66 (43%) patients required more than 18 months.

In MSSA group 8(67%) out of 12 patients united within 18 months and 4(33%) patients required more than 18 months. But in rest of the group (MRSA, ESBL and combined) more than 40% of the fracture took more than 18 months to unite.

Soft tissue procedure:

Soft tissue coverage procedure included both local rotation flap and muscular flap. Total 21(14%) patients requiring flap cover, all the patients were from infected non unions of the tibia and none from femur group.

Soft tissue coverage procedures were maximum in the fourth category in co infections of MRSA and ESBL 5(19%) and least in MSSA group 1(8%).

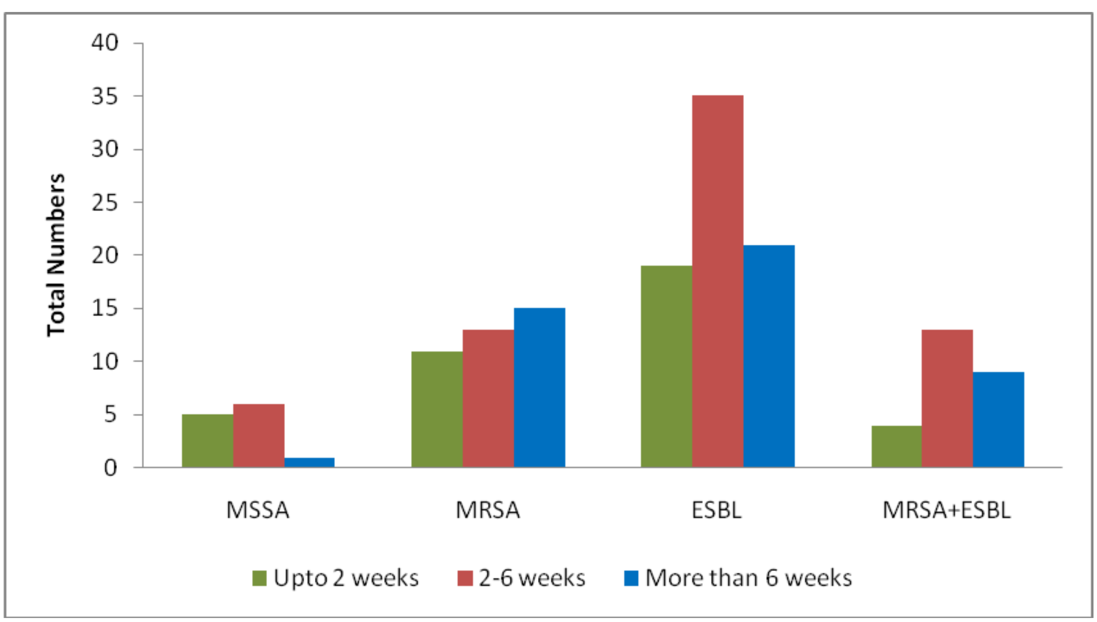
Number of secondary procedure:

In our study 123(83%) patients required secondary procedure (minor procedures 59 and major 64) after the definitive fixation. The maximum number of secondary procedure are done in fourth category in co infections of MRSA and ESBL 22(92%), next is ESBL63(84%), then MRSA 30(81.0%) and least in MSSA group 8(66.7%).

Secondary out comes

		MSSA(12)	MRSA(39)	ESBL(75)	MRSA+ESBL(26)	TOTAL(152)
Total duration of IP admission	Up to 2wks	5(42%)	11(28%)	19(25%)	4(15%)	39(26%)
	2-6wks	6(50%)	13(33%)	35(47%)	13(50%)	67(44%)
	>6wks	1(8%)	15(39%)	21(28%)	9(35%)	46(30%)
IP economic cost	Up to 0.75L	10(83%)	18(46%)	43(57%)	11(42%)	82(54%)
	0.76-2L	2(17%)	19(49%)	24(32%)	11(42%)	56(37%)
	>2L	0	2(5%)	8(11%)	4(17%)	14(9%)

Total duration of IP admission



Secondary out comes of the study

(1) Duration of in patient(IP) admission

(2) In patient (IP) economic cost

Duration of in patient admission:

It ranges from 1 weeks to 20 weeks but according to table more than 75% of the patients with infected non union had hospital stay more than 2weeks. But within the groups it is unevenly distributed, there is only one patient(8.3%) in MSSA group who required total duration more than 6weeks of hospital but in MRSA group 15(39%), ESBL group 21(28.0%) and 9(35%) in combined MRSA and ESBL group.

In patient (IP) economic cost:

According to table 83 percentage of patients with MSSA had final bill less than or equal to seventy five thousands , but in MRSA group 54 percentage of the patients had final bill more than seventy five thousand, similarly in ESBL group 43 percentage patients had final bill more than seventy five thousand and in MRSA and ESBL group 58 percentage. Interestingly none of the patients in MSSA group had final bill more than 2 lakhs

Complications

	MSSA(12)	**MRSA(39)**	**ESBL(75)**	**MRSA+ESBL(26)**	**TOTAL(152)**
Poor regenerate	2(17%)	12(32%)	22(29%)	9(38%)	45(30%)
Pin tract infection	8(67%)	28(73%)	56(75%)	21(83%)	113(75%)
Infection need change of wire/frame	1(8%)	5(14%)	4(5%)	5(21%)	15(10%)
Wire breaking	0	1(3%)	2(3%)	1(4%)	4(3%)
refracture	0	6(15%)	7(9%)	3(12%)	16(11%)
Fracture of regenerate	0	4(11%)	2(3%)	1(4%)	7(5%)
Chronic osteomyelitis	2(17%)	5(14%)	24(32%)	7(29%)	38(26%)
Persistent PTI	0	1(3%)	11(15%)	0	12(8%)

Complications

Among complications pin tract infection was present in 113(75.0%) patients but its distribution was uniform among the organisms. But persistent of pin tract infection mainly seen in ESBL(15%) and MRSA(3%) and none of the MSSA and co infection of MRSA and ESBL had persistent of pin tract infection.

Discussion

Infected non union is still an extremely difficult clinical problem despite of the major advancement in the fixation technique, soft tissue management, and antibiotic therapy.

The infection at the fracture site not only prevents the stable internal fixation but also delays fracture healing. The combination of the mechanical instability and infections at the fracture site provides an unfavorable condition for fracture healing . If the infection is not controlled the fracture healing process eventually arrest.

Debridement is the most important step in the treatment of the infection. After debridement bone reconstruction can be done by different methods mentioned earlier.

This study describes the clinical, radiological and functional out come of the infected non union of the lower limb affected with different types of organism namely MSSA, MRSA, ESBL and co infection with MRSA and ESBL.

There is no study in the literature which compares different types of organisms and their clinical, radiological and functional out come in infected non unions of long bones.

There are studies conducted in prosthesis joint infection with different staphylococcus namely MSSA, MRSA and CoNS and their out come and similar study in surgical site infections(SSI) in general.

The purpose of this study was to compare different types of organism namely MSSA,MRSA and ESBL and their outcomes in infected non unions of long bone lower limbs.

Bone results using ASAMI score:

Bone results were available in all the 152 patients. Among them 66(44%) patients had excellent to good results and 86(57%) had fair to poor results.

Goldstrohm et al treated 39 patients of infected non union tibia with bone defect with Ilizarov fixator and they had only 61 percent rate of success. **Paley et al** reported 90 to 97 percentage of success rate in infected non unions of tibia. Our results are inferior to results mentioned in the literature. But out main objective was to compare the organism and their our come.

In individual category patients with MSSA 8(67%) had excellent to good out come. 31(80%) patients with MRSA and 21(81%) patients with combined MRSA and ESBL had fair to poor out come.

This was statistically significant (p value 0.0). This supports our initial hypothesis that MRSA and ESBL are more virulent than MSSA.

Functional results were studied using ASAMI score:

In our study we had 31 patients in which functional results were available. Among them 18(58%) patients had excellent to good results and 9(29%) patients had fair to poor results. Total 4(13%) patients had undergone amputation. Among individual categories all the patients with MSSA has excellent to good results. In MRSA category 4(44%) patients had excellent to good results and 2(22%) patients had fair to poor results. In ESBL category 10(71%) patients had excellent to good results and 4(28.6%) had fair to poor results. In co infection of MRSA and ESBL 2(33.3%) patients had excellent to good results and 3(50.0%) patients had fair to poor results.

In contrast to **Dendrinos et al** results our results showed functional results were better than bone results. Among bone results 66(44%) patients had excellent to good results and 86(57%) had fair to poor results and in functional results 18(58%) patients had excellent to good results and 9(29%) patients had fair to poor

Resolution of infection:

Our study showed that in infected non union of the lower limbs complete cure from the infection can be achieved in 85% of the patients(129/152). In individual group MSSA has cure rate of 92% (11/12), MRSA has 74% (29/39), ESBL has 92% (69/75) and co infection of MRSA and ESBL has 77% (12/26). The cure percentage is highest for the MSSA group and ESBL group, then co infection of MRSA and ESBL group and least in MRSA group

Though it is statistically not significant(p value 0.5) our study showed that in patients with infected non union with MRSA there is high chance of persistence infections compared to non union with MSSA and ESBL Our results are comparable to the study done by **Dorota Teterycz et al** (31)

In comparisons of different staphylococci in orthopedic implant infections, they divided orthopedic implant infection into three group MSSA, MRSA and CoNS. It was a retrospective study included 44 patients of MRSA, 58 patients of MSSA, and 61 patients of CoNS. Overall cure was achieved in 57% of MRSA infections, 72% of MSSA infections, and 82% of CoNS infections. In the subgroup of arthroplasty infections cure was achieved in 39% of MRSA, 60% of MSSA, and 77% of CoNS.

They concluded that in orthopedic implant infections over all S. aureus is more virulent than CoNS. And among MSSA and MRSA,MRSA has the worst outcome.

In our study 129(85%) patients had complete cure of infection and only in 23(15%) patients infection had persisted. We compared number of debridement and resolution of infection. Out of 23 patients who had persisted infection, 10 patients had upto two debridement and 13 patients had more than two debridement. It showed that there is no co relation between number of debridment and resolution of infection.

We also compared antibiotic bead application and resolution of infection. Total 21 patients had debridement and antibiotic beads applications among them 20(95%) patients had complete resolution of infection.

We had 11 patients with malnutrition among them 8(73%) had complete resolution and 3(27%) had in complete resolution of infection which was not statistically significant (p value 0.5)

Similarly we had 17 patients with diabetes among them 16(94%) patients had complete resolution of infection.

Union

Out of 152 patients in 132(87%) patients fracture had completely united. There was no much difference in the percentage of union among the different organism and union is seen in 85% of the fracture Since there are no studies in the literature which compares the organisms and fracture union in infected non union of the long bone, we can not compare our results with other studies, but according to this study in our hospital there is no difference in the fracture union percentage in different organism groups. With overall union rate of 87% (132/152) this union percentage is good.

In patients treated with Ilizarov fixator union percentage was 88% (66 /75) and in patients treated with Orthofix union percentage was 87% (60/69), not much of difference among the groups.

In study by **Dendrinos et al** (33) infected non union of tibia treated with Ilizarov fixator he had 28 cases of non union tibia, 25cases out of 28 united(89.7%) this comparable to our treatment results

Marschall Berkes et al (34) did a study on postoperative infections following internal fixation of the fracture, with different organism and maintenance of hardware. They had 123 patients of post operative infection following fracture fixation in early post operative period less than 6 weeks. End result was measured as rate of osseous union and clearance of infection. They found that osseous union in 78.8% with patient with MSSA infection, 65% with patients with MRSA infection and 66.6% with protease mirabilis infection(ESBL group). Though this study was conducted in early post operative infection ,the end results were measured as bone union and clearance of infection.

Percentage of union and clearance of infections mentioned in this study were comparable to our results.

Number of debridement

Our study showed that number of debridement in infected non union with MRSA , ESBL and co infection of MRSA plus ESBL more than the MSSA group, we believe this is due to MRSA is more invasive, more virulent and more difficult to eradicate from the bone and soft tissue.

Post debridement bone loss:

We started our study with hypothesis that if the organism is more virulent, damage and spread of infection is more in both soft tissue and bone. This was showed in our results.

Out of 152 patients 62(42%) patients had undergone bone resection up to 30mm and 87(58%) patients required more than 30mm bone resection to completely remove the necrotic tissue. Thus about 60 percent of our patients had more than 30mm post debridement bone loss.

Within the groups 58 percentage of MSSA group had less than 30mm of post debridement bone loss, and more than 65 percentage of patients with MRSA and co infection of MRSA and ESBL had more than 30mm of post debridement bone loss.

Though this is not statically significant (p value 0.33) we can say that patients MSSA has less post debridement bone loss compared to other group

Bone graft:

Among 152 patients 51(34%) patients requited bone grafting procedure.

It indirectly reflects the debridement and post debridement bone loss. Percentage of bone grafting was highest in co infection of MRSA and ESBL 10(40%) and lowest in MSSA group 2 (17%). Compared to MSSA all other group has double the number of bone grafting procedure.

There is no difference in the Ilizarov and Orthofix group in terms of percentage of bone graft(33.8% both).among 16 patients with diabetes only 5(31%) patient had bone grafting. Out of 5 smokers 3(60%) had bone grafting. These values were small and conclusion can not be drawn.

In study by **Dendrinos et al** (33) infected non union tibia treated with Ilizarov fixator, they had 28 cases of non union, three patients required bone graft augmentation to unite fracture(11%).

Refracture:

In our series out of 152 patients 16(11%) patients had refracture. Refracture percentage was highest in MRSA group about15%(6/39), none of the MSSA group had refracture.

Lalit Maini et al (35) treated thirty patients of infected non unions of the long bone with Ilizarov fixator ,they reported that bone grafting at the docking site was required in three patients(10%), three patients of refracture (10%) and three patients of recurrence of infection (10%).

Results of these study were comparable to our study.

Time to union:

Overall in 79(52%) patients fracture united within 18 months of period and 66 (43%) patients required more than 18 months.

This was quite high compared to other studies, but there was notable difference If we compare time to union with **Dendrinos et al** (33) results, they eradicated the infection before applying the Ilizarov fixator, their mean duration of the treatment was 10 months after application of Ilizarov and mean time to union was 6 months, but they calculated mean time to union from the day that the intercalary segment came in contact with the target segment which was six months.

We have treated our patients with not only with Ilizarov fixator but also with limb reconstruction system (Orthofix), internal fixation with or without antibiotic beads and we defined our time to union from the first day of primary treatment and definite fixation and not from the day when intercalary segment came in contact with target segment.

In MSSA group 8(67%) out of 12 patients united within 18 months and 4(33%) patients required more than 18 months. But in rest of the group (MRSA, ESBL and combined) more than 40% of the fracture took more than 18 months to unite.

Fracture union is complex process, is affected by local and systemic factors, infection at the fracture site is clearly one of the major factor. Though it is statistically not significant (p value 0.59), according to our observation upto 70% of the patients with MSSA united within 18 months and more than 40% fracture affected with MRSA,ESBL and combined poly microbial required more than 18 months for the fracture union.

In our study most of the patients were from patients coming from other states (70%). By the time they come to us they already had under gone 2-3 procedure, debridement of bone , gap at fracture site, infection , bad soft tissue and scared limb with recalcitrant non union. This also explains our union time.

Soft tissue procedure:

Soft tissue coverage procedure included both local rotation flap and muscular flap, out of 21(13.5%) patients requiring flap cover all the patients were infected non unions of the tibia and none from the femur group.

Soft tissue coverage procedures were maximum in the fourth category in co infections of MRSA and ESBL 5(19%) and least in MSSA group 1(8%). Again we can explain this with the same hypothesis that if the organism is more virulent, damage and spread of infection is more in both soft tissue and bone

Number of secondary procedure:

In our study 123(83%) patients required secondary procedure (minor procedures 59 and major 64). The maximum number of secondary procedure are done in fourth category in co infections of MRSA and ESBL 22(92%), next is ESBL63(84%), then MRSA 30(81%) and least in MSSA group 8(67%)

Amputation: Out of 4 cases of amputation 3 belong to MRSA group and one to co infection of MRSA and ESBL group.

Out of four patient three patients underwent amputation as primary procedure. Two out of three patient underwent primary amputation had large exposed, necrotic bone with poor soft tissue. Third patient already had below knee amputation with infected stump, poor soft and with flexion contracture which was revised to above knee amputation.

One patient initially treated with four debridment and external fixation then applied Ilizarov but due to active discharging sinus, pin tract infection,long duration of treatment (more than 4 years) and unstable knee after ilizarov exit required amputation.

Secondary out comes

Duration of in patient (IP) admission:

It ranges from 1 week to 20 weeks but according to table more than 75% of the patients with infected non union had hospital admission more than 2weeks. But within the groups it is unevenly distributed. There was only one patient (8%) in MSSA group who required total duration more than 6weeks but in MRSA group there were 15(40%), ESBL group 21(28%) and 9(35%) in combined MRSA and ESBL.

From above we can conclude that MRSA, ESBL and co infection of MRSA and ESBL had more number of hospital comparative to MSSA.

We believe this is because MRSA and ESBL are more virulent compared to MSSA and it more difficult to eradicate the infection in these groups, hence needs multiple debridement, more number of surgical interventions that indirectly increases the total duration of hospital stay.

Deverick et al (37) studied clinical and financial out come in patients with surgical site infections, they studied 659 surgical patients among them 150 were MRSA and 128 were MSSA. Most of these patients were orthopedic patients (MRSA 69,MSSA 95). They found that SSIs due to MRSA lead to significant patient suffering , 7-fold increased risk of death, 35-fold increased risk of hospital readmission, more than 3 weeks of additional hospitalization, and more than $60,000 of additional charges compared to uninfected controls. This study represents the largest study to date of outcomes due to SSI due to MRSA.

Cost of the treatment:

This includes the total cost of the treatment including intravenous antibiotic, surgical procedures including implant charges. According to table 83% (10/12) patients with MSSA had final bill less than or equal to seventy five thousand, but in MRSA group 54%(21/39) patients had final bill more than seventy five thousand, similarly in ESBL group 43%(32/75) patients had final bill more than seventy five thousand and in MRSA and ESBL group 59%(15/26). Interestingly none of the patients in MSSA group had final bill more than 2 lakhs.

Our observations are similar to the study conducted by **Deverick et al** (37)

Complications:

Among complications pin tract infection was present in 113(75.0%) patients but its distribution was uniform among the organisms. But persistent of pin tract infection mainly seen in ESBL(15%) and MRSA(3%) and none of the MSSA and co infection of MRSA and ESBL had persistent of pin tract infection.

Madhusudhan et al (38) studied 22 patients with infected non union of tibia treated with Ilizarov fixator and reported similar complication rate. They had pin tract infection in all the patients(100%), poor regenerate in 2 (9%)patients, infection needing change of frame or wire in 4(18%) patients, chronic osteomyelitis in 6 (27%)patients and persistent pin tract infection in 4 patients(18%).

Pin tract infection was uniformly distributed in patients and there was no difference in patients with good and poor bone results. 72% (48/113) patients had excellent to good results and 75%(65/113) patients had fair to poor results. Also there was no difference in the pin tract infection and diabetes.

Case Profile

Case 1

18 years old college student presented to casualty with 10 days old open fracture of right femur with closed both bone leg fracture. Initial underwent debridement and external fixation both femur and tibia. 6 months later presented with infected non union of right femur. Undergone debridement and Orthofix application, 2 months later debridement and bone marrow injection

Time to union 8 months

No shorting, knee flexion 0-140,

No angulation, fracture united

Bone results: good (bone marrow injection)

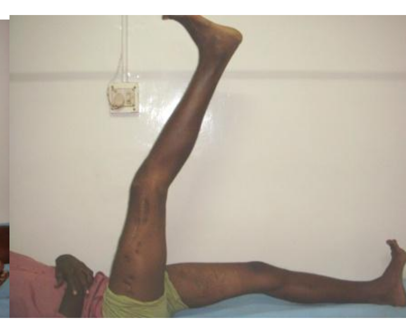
Functional result: excellent

24/04/2009

05/10/2009

18/06/2010

28/11/2011



Case 2

47 year old gentleman presented 2 days after RTA with open (IIIB)fracture of left proximal tibia, initially debridment and wash out was done. After 4 days under went debridement and internal fixation with T plate, external fixation and reverse sural artery flap. 2 months later presents with exposed implant and undergone local rotation flap. Infection persisted,4 months later implant exit and ilizarov fixator.22 months later fracture ilizarov exit and b/k cast.27 months later bone graft .

Time to union18 months

No shorting, knee flexion 5-140

No angulation, fracture united

Bone results: good(bone graft)

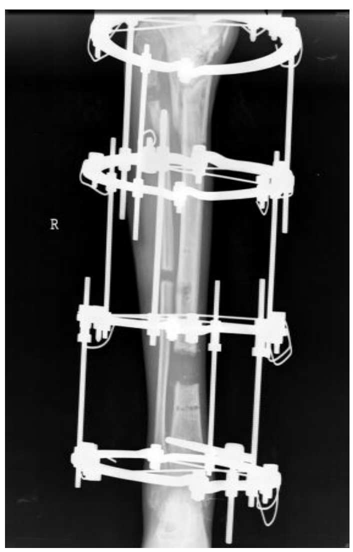
Functional result: excellent

12/06/2006

01/10/2006

13/02/2007

03/06/2008



Limitations of the study

This was the retrospective study conducted to compare clinical, radiological and functional out come in infected non unions of long bone lower limbs among different organism namely MSSA, MRSA and ESBL. Presently there are no studies in the literature which compare clinical radiological and functional out come in infected non union among these organisms.

We have collected data of all patients of infected non union lower limbs treated in CMC between year 2007 to 2009. Limitations of this study were

1) This is a retrospective study and our data was based on out patient(OP), in patient(IP) records, operation records. As with other retrospective study complete reliability of data may be questionable.

2) This study included all the patients with infected non union long bone lower limbs treated in CMC, both femur and tibia. Methods of treatment were debridement and internal fixation, limb reconstruction system(Orthofix) and Ilizarov fixator. Thus our treatment methods are not uniform.

3) In this study we included all the patients from different units and there are too many number of surgeons involved in the treatment.

4) The experience of the surgeons and quality of debridement also were limiting factors.

5) Distribution of the organisms in patients were not uniform, more patients belong to ESBL and MRSA group and less patients in MSSA group.

6) Less number of patients were available for assessing the functional results (only 31 patients were available for functional results analysis).

Conclusion

Infected non union is still an extremely difficult clinical problem despite of the major advancement in the fixation technique, soft tissue management, and antibiotic therapy.

In this study we found out clinical and functional out comes of the patients with infected non of union lower limb long bones.

(A) In comparing our bone results with bone results mentioned in literature we found that our bone results are inferior to those mentioned in the literature. We had 66 (44%) patients with excellent to good results and 86 (57%) patients with fair to poor results.

(B) But our percentage of fracture union (87%) and resolution of infections (85%) was good and similar to other studies. Our functional results are slightly better than bone results. We had 18(58%) patients with excellent to good results and 9(29%) patients with fair to poor.4(13%) patients underwent amputation

(C) In comparison between MSSA, MRSA, ESBL and co infection of MRSA and ESBL we found that except for percentage of fracture union (85%) which was similar in all the four groups, rest of the categories show major difference. Resolution of infection was 92% in MSSA compared to 74% in MRSA. Similarly number of debridement and post debridement bone loss were more in MRSA and ESBL group compared with MSSA. MSSA group had no refracture and time to union was shortest compared to other group(67%within 18 months). Similarly soft tissue cover procedure and number of secondary procedure required were less in MSSA group compared to other group and also number of days of hospital admission and total cost of the treatment is substantially less in MSSA group

(D) In complications also we saw that poor regenerate, pin tract infection, infection which needs change of wire/frame and persistent pin tract infection percentages are more in MRSA and ESBL group compared to MSSA group.

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Clinical audit to compare and study the detection of Mycobacterium tuberculosis by Mycobacteria Growth Indicator Tube (MGIT) , Lowenstein Jensen(LJ) media and direct AFB smear examination by Ziehl–Neelsen(ZN) stain in tubercular spondylodiscitis treated in Department of Spinal Disorders Surgery(SDS) Unit, Christian Medical College ,Vellore between 2008 to 2012

An Audit submitted to the Tamil Nadu Dr M.G.R. Medical University in partial fulfillment of the requirement for the award of M.S. Branch II (Orthopedic Surgery) Degree March 2010-2013

Submitted by Dr Raju L Hadimani PG Registrar

Guide:

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Clinical audit to compare and study the detection of Mycobacterium tuberculosis by Mycobacteria Growth Indicator Tube (MGIT) , Lowenstein Jensen(LJ) media and direct AFB smear examination by Ziehl–Neelsen(ZN) stain in tubercular spondylodiscitis treated in Department of Spinal Disorders Surgery(SDS) Unit, Christian Medical College ,Vellore between 2008 to 2012

Title of the study: A comparative study for the detection of Mycobacterium tuberculosis by MGIT , Lowenstein Jensen(LJ) media and direct AFB smear examination by Zeihl-Neelsen(ZN) stain.

Aims and objective:

(1) To compare the sensitivity of detection of AFB in tubercular spondylodiscitis between LJ media and MGIT media.

(2) To find out whether there is any increase in the number of cases of tubercular spondylodiscitis after the introduction of MGIT technique.

(3) To find out prevalence of TB spondylodiscitis in SDS unit.

Hypothesis: Efficiency of detection of Acid Fast Bacilli (AFB) in tubercular spondylodiscitis between LJ media and MGIT media are same.

Inclusion criteria

(1) All patients of tubercular spondylodiscitis treated in Spinal Disorders Surgery Unit between 2008 to 2012 are included in the study.
(2) Cases with biopsy positive and/or culture positive and/of smear positive for Mycobacterium tuberculosis were included in the study

Exclusion criteria:

(1) Post operative spondylodiscitis were excluded from study

(2) Post operative implant infection were excluded from study

(3) Patients with negative biopsy, negative smear and negative culture

(4) Patients with healed and treated TB who had elective implant exit.

(5) Pyogenic and fungal spondylodiscitis.

Review of literature:

The **Lowenstein–Jensen medium**, more commonly known as **LJ medium**, a solid media, is a growth medium specially used for culture of **Mycobacterium**, notably Mycobacterium tuberculosis. When grown on LJ medium, M. tuberculosis appears as brown, granular colonies (sometimes called "buff, rough and tough"). The media must be incubated for a significant length of time, usually four weeks, due to the slow doubling time of M. tuberculosis compared with other bacteria (15–20 hours).

Mycobacteria Growth Indicator Tube (MGIT)

MGIT stands for Mycobacteria Growth Indicator Tube, and 960 indicates the total number of culture tubes it can hold at any given time. The BACTEC MGIT 960 System is an in vitro diagnostic instrument for rapid detection of Mycobacteria in clinical specimens other than blood.

The system is designed to meet the needs of medium and high volume labs, capable of processing about 8,000 cultures per year. This system is simple, efficient , safe to use and occupies small laboratory space.

Materials and methods:

Retrospectively data was collected from all patients of Tubercular spondylodiscitis treated in SDS between 2008 to 2012.Total of 193 patients with tubercular spondylodiscitis were included(121 males and 72 females), mean age of patients 35.95years(range from 3 to 71 years) were included in the study.

Definitions :

Tubercular spondylodiscitis is defined as patients with infective focus in the spine with biopsy suggestive of M. tuberculosis and/or smear positive and/or culture positive.

Cervical region included from C1 to C6, Cervico-Thoracic junction between C7 andT1, Thoracic spine divided in to upper Thoracic(T2-T6) and lower Thoracic spine(T7-T10), Thoraco-lumbar junction from T11,T12 and L1, lumbar region from L2 L5 and sacral region.

Collections of specimen:

Collected specimen was divided in to three categories. First category was open biopsy or surgical specimen , second category was from CT guided biopsy specimen and third category is specimen collected from Ultrasound guided biopsy specimen.

Detection of AFB:

All patients with scanty AFB to any number of AFB were considered as smear positive.

Culture positivity is defined as all the patients who has grow AFB in any of the media(LJ or MGIT media) irrespective of sensitivity and resistance.

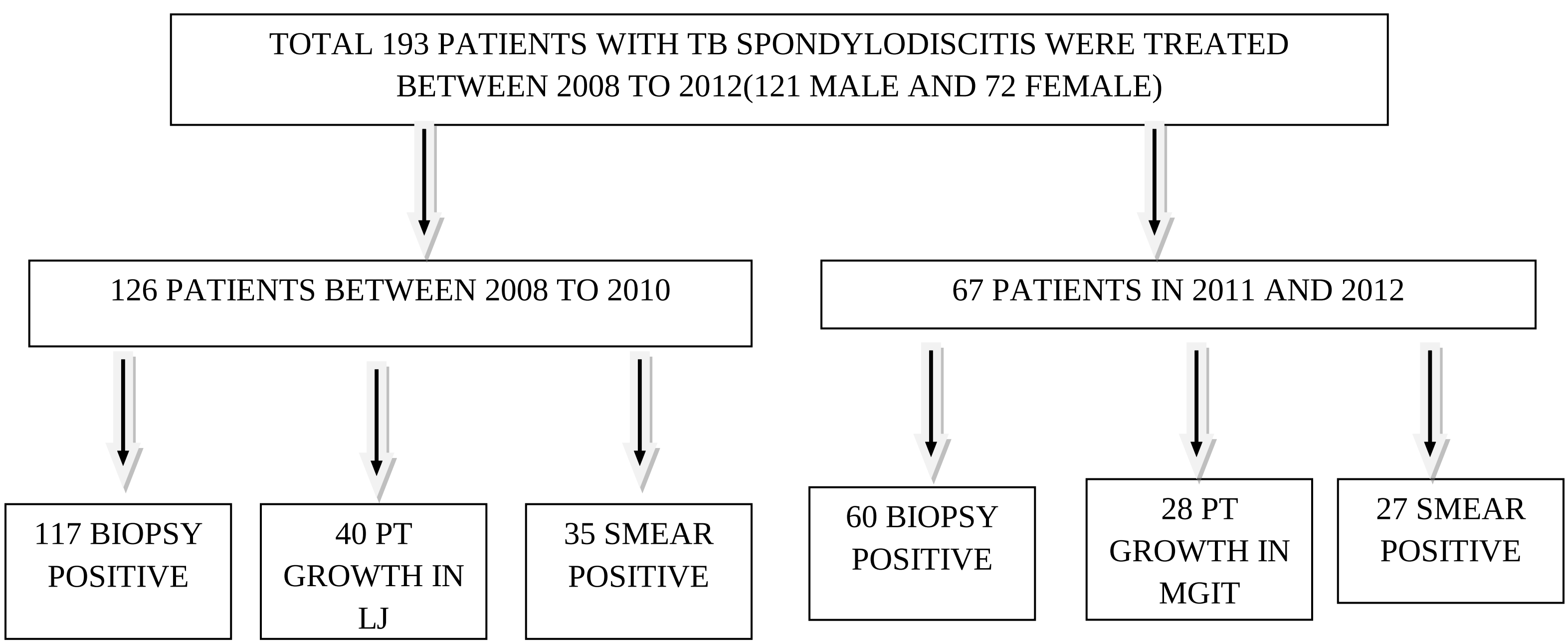
Biopsy positivity is defined as all the patients who has shown AFB, caseating granuloma, multinucleated giant cells, Langhans giant cell, epithelioid cell, histiocytes, organized collection of macrophages.

Patients for the treatment purpose considered to have tuberculosis infection if one of the above mentioned criteria is fulfilled(Either biopsy positive or smear positive or culture positive).

But to calculate the sensitivity of detection of solid media(LJ) against liquid media(MGIT) we considered biopsy as gold standard and all the patients with biopsy negative were excluded in calculating the sensitivity.

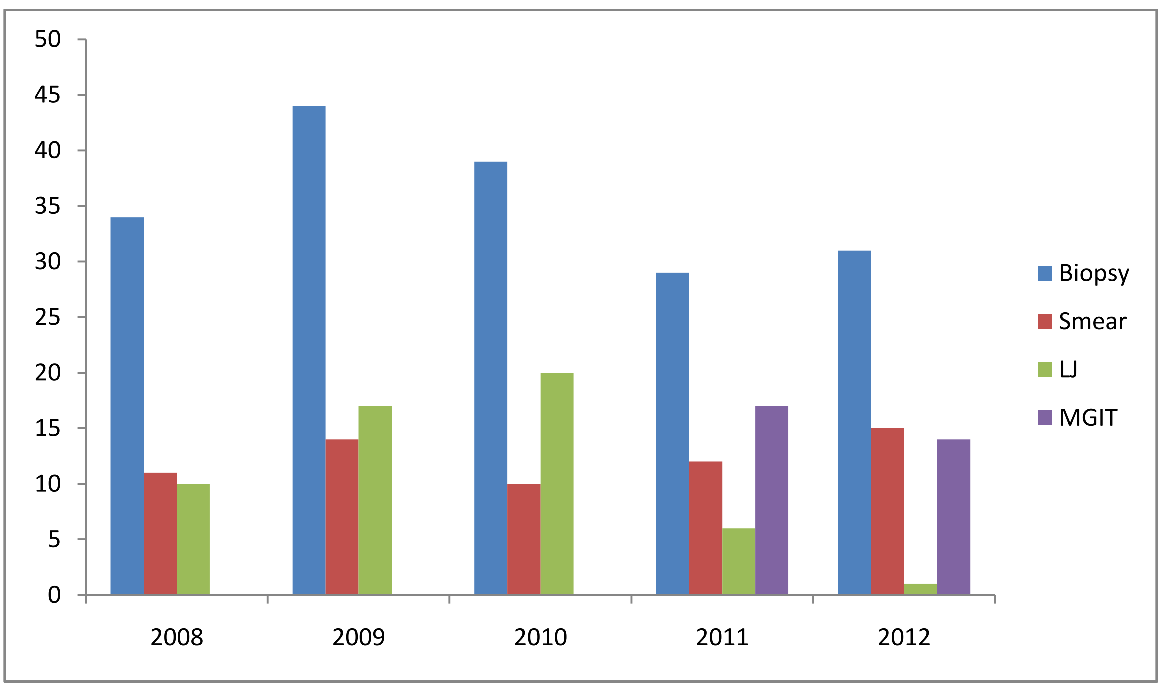
SDS unit started requesting for MGIT culture since 2011 in Christian Medical college, Vellore. We divided our patients in two to groups, group one all the patients with biopsy positive for tuberculosis who are also positive for culture by LJ media, this group mainly includes patients from 2008 ,2009 and 2010 and second group includes patients positive for biopsy and also positive for culture by MGIT, this group mainly includes patients from 2011 and 2012.

Results and Observations:



YEAR	Cervical	C7-T1	T2-T10	T11-L1	L2-L5	Multiple	Total
2008	0	0	18	8	9	4	39
2009	0	0	17	10	20	1	48
2010	0	1	12	13	12	1	39
2011	0	0	8	11	8	3	30
2012	2	2	13	10	9	1	37
	2	3	68	52	58	10	193

Number of patients



Sensitivity of LJ media growth in biopsy positive patients = total number of patients with LJ positive divided by total number biopsy positive of patients X 100(40/126 X100=**34%**)

Sensitivity of MGIT media growth in biopsy positive patients = total number of patients with MGIT positive divided by total number biopsy positive of patients X 100(27/60 X100=**46%**)

Smear positivity = total number of smear positive patients divided by total biopsy positive patients X 100(62/193X100=**32.1%)**

In our study dorsal spine (T2-T10) was the most commonly affected spine in 68 patients(35%),followed by lumbar spine 58 patients(30%) and Thoroco-lumbar junction 52 patients(26%).

Multiple level spine involved in 10 patients (5%) mainly dorsal and lumbar spine

Total 162 open biopsy, 20 CT guided biopsy and 11 ultrasound guided biopsy were done.

Discussion:

The present study demonstrated that MGIT system provided better isolation rate of *Mycobacteria* (46%) from a variety of clinical samples than the LJ media (34%).The difference sensitivity was 12% which is statistically not significant(P value 0.08) though it was clinically significant.

Various authors have reported similar findings ranging from 80 to 100% for M960 and from 59.7 to 87.2% for LJ (1,2,3).

There is no study in the literature which compare the sensitivity of the detection of AFB in tubercular spondylodiscitis by LJ media and MGIT media. Most of the studies were done in patients with pulmonary tuberculosis. Their case definition and testing of the sensitivity is quite different from our study.

RESULTS OF MGIT Vs. LJ FROM OTHER RESEARCHERS

Study	Conventional culture	BACTEC system
Zanetti et al 1997	69.3%	95%
Jesus et al 2001	46.6%	86.6%
Lu et al 2002	45.5%	71%

Recovery rates from positive sample

Limitation of the study:

(1) Distribution of the infective focus in spinal column is not uniform.

(2) Amount of material available for the study is not uniformly distributed with limited amount from cervical and dorsal region and sufficient amount a lumbar spine

(3) History of prior treatment not taken in to consideration.

CONCLUSION:

Diagnosis of TB depends on the isolation and identification of Mycobacteria and the control of MDR tuberculosis depends rapid sensitivity results. Therefore use of sensitive methods and faster culture methods like the BACTEC MGIT system is necessary

Though difference in Sensitivity of both test not statistically significant, in order to get P value less we should increase our sample size by studying more number of patients.

ACKNOWLEDGEMENT: Analysis of data by Dr Jayasheelan professor Biostatistics

Department CMC Vellore

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INSTITUTIONAL REVIEW BOARD (IRB)
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Additional Vice Principal (Research)

December 4, 2012

Dr. Raju L Hadimani
PG Registrar
Department of Orthopaedics
Christian Medical College
Vellore 632 004

Sub: **Fluid Research grant project NEW PROPOSAL:**
The clinical, functional and radiological outcome of infected non union of long bones lower limb, above the age of 18 years Retrospective cohart study comparing outcome of MSSA,MRSA AND ESBL.
Dr. Raju L Hadimani, Orthopeadics, Dr. Manasseh N, Dr. Vinoo Mathew Cherian, Orthopeadics.

Ref: IRB Min. No. 7907 dated 4.7.2012

Dear Dr. Raju L Hadimani,

I enclose the following documents:-

1. Institutional Review Board approval
2. Agreement

Could you please sign the agreement and send it to Dr. Nihal Thomas, Addl. Vice Principal (Research), so that the grant money can be released.

With best wishes,

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

CC: Dr. Manasseh, Department of Orthopaedics

Dr Nihal Thomas
MBBS MD MNAMS DNB (Endo) FRACP(Endo) FRCP(Edin)
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Dr. Raju L Hadimani, Orthopaedics, Dr. Manasseh N, Dr. Vinoo Mathew Cherian, Orthopeadics.

Ref: IRB Min. No. 7907 dated 4.7.2012

Dear Dr. Raju L Hadimani,

The Institutional Review Board (Blue, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project entitled "The clinical, functional and radiological outcome of infected nonunion of long bones lower limb, above the age of 18 years Retrospective cohart study comparing outcome of MSSA,MRSA AND ESBL." on July 4, 2012.

The Committees reviewed the following documents:

1. Format for application to IRB submission
2. Informed consent Form (English, Tamil, Hindi, Bengali)
3. Proforma
4. Cv's of Drs. Raju L Hadimani,Manasseh N, Vinoo Mathew Cherian.
5. A CD containing documents 1 - 4

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Additional Vice Principal (Research)

The following Institutional Review Board (Research & Ethics Committee) members were present at the meeting held on July 4, 2012 in the CREST/SACN Conference Room, Christian Medical College, Bagayam, Vellore 632002.

Name	Qualification	Designation	Other Affiliations
Dr. B.J. Prashantham	MA (Counseling), MA (Theology), Dr Min(Clinical)	Chairperson(IRB)& Director, Christian Counselling Centre	External, Scientist
Mrs. S. Pattabiraman	BSc, DSSA	Social Worker, Vellore	External, Social Scientist
Mr. Sampath	BSc, BL	Advocate	External, Advocate
Dr. Vinitha Ravindran	MSc, Ph.D	Professor, Child Health Nursing, CMC.	Nurse
Dr. Jayaprakash Muliyil	BSC, MBBS, MD, MPH, DrPH(Epid), DMHC	Retired Professor, Vellore	External, Scientist
Mr. Joseph Devaraj	BSc, BD	Chaplain, CMC	Lay Person
Dr. Priya Abraham	MBBS, MD, PhD	Professor, Virology, CMC	Clinician
Dr. Susanne Abraham	MBBS, MD	Professor, Dermatology, Venerlogy & Leprosy, CMC.	Clinician
Dr. Anil Kuruvilla	MBBS, MD, DCH	Professor, Neonatology, CMC.	Clinician
Dr. Bobby John	MBBS, MD, DM, PhD, MAMS	Professor, Cardiology, CMC.	Clinician
Dr. Benjamin Perakath	MBBS, MS, FRCS	Professor, Surgery (Colorectal), CMC.	Clinician
Dr. Paul Ravindran	PhD, Dip RP, FCCPM	Professor, Radiotherapy, CMC	
Dr. Sujith Chandy	MBBS, MD	Professor, Pharmacology & Clinical Pharmacology, CMC.	Clinician
Dr. Denny Fleming	BSc (Hons), PhD	Honorary Professor, Clinical Pharmacology, CMC.	

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Additional Vice Principal (Research)

Dr. Ranjith K Moorthy	MBBS MCh	Professor, Neurological Sciences, CMC	Clinician
Dr. Nihal Thomas	MD MNAMS DNB(Endo) FRACP(Endo) FRCP(Edin)	Secretary IRB (EC)& Dy. Chairperson (IRB), Professor of Endocrinology & Addl. Vice Principal (Research), CMC.	Clinician

We approve the project to be conducted as presented.

The Institutional Ethics Committee expects to be informed about the progress of the project, any serious adverse events occurring in the course of the project, any changes in the protocol and the patient information/informed consent. And on completion of the study you are expected to submit a copy of the final report.

Yours sincerely,

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

Dr Nihal Thomas
MBBS MD MNAMS DNB (Endo) FRACP(Endo) FRCP(Edin)
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CC: Dr. Manasseh, Department of Orthopaedics

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